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(54) Title: NOVEL HUMAN VOLTAGE-GATED POTASSIUM CHANNEL (57) Abstract <p>The present invention is directed to novel human DNA sequences encoding a voltage-gated potassium channel, KCNQ5, located in a chromosomal region that contains a gene associated with Stargardt-like macular dystrophy, cone-rod macular dystrophy, and Salla disease.</p>		

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TITLE OF THE INVENTION

NOVEL HUMAN VOLTAGE-GATED POTASSIUM CHANNEL

CROSS-REFERENCE TO RELATED APPLICATIONS

5 Not applicable.

STATEMENT REGARDING FEDERALLY-SPONSORED R&D

Not applicable.

10 REFERENCE TO MICROFICHE APPENDIX

Not applicable.

FIELD OF THE INVENTION

15 The present invention is directed to novel human DNA sequences encoding a voltage-gated potassium channel.

BACKGROUND OF THE INVENTION

Voltage-gated potassium channels form transmembrane pores that open in response to changes in cell membrane potential and selectively allow
20 potassium ions to pass through the membrane. Many voltage-gated potassium channels have been identified. They are distinguishable by tissue-specific patterns of expression as well as by electrophysiological and pharmacological properties.

Voltage-gated potassium channels have been shown to be involved in maintaining cell membrane potentials and controlling the repolarization of action
25 potentials in many cells, *e.g.*, neurons, muscle cells, and pancreatic β cells. They are important targets for drug discovery in connection with a variety of diseases.

Functional voltage-gated potassium channels are believed to be tetramers of four alpha subunits, each of which contains six transmembrane spanning segments. The alpha subunits making up a tetramer may be the same (in the case of
30 homotetramers) or may be different (in the case of heterotetramers). The membrane-spanning alpha subunits making up the tetramers may sometimes be associated with additional, beta subunits, which may alter the behavior of the tetramers.

For reviews of voltage-gated potassium channels see Robertson, 1997, Trends Pharmacol. Sci. 18:474-483; Jan & Jan, 1997, J. Physiol. 505:267-282; Catterall, 1995, Ann. Rev. Biochem. 64:493-531.

Macular dystrophy is a term applied to a heterogeneous group of diseases that collectively are the cause of severe visual loss in a large number of people. A common characteristic of macular dystrophy is a progressive loss of central vision resulting from the degeneration of the pigmented epithelium underlying the retinal macula. In many forms of macular dystrophy, the end stage of the disease results in legal blindness. More than 20 types of macular dystrophy are known: e.g., age-related macular dystrophy, Stargardt's and Stargardt-like macular dystrophy, cone-rod dystrophies, atypical vitelliform macular dystrophy (VMD1), Usher Syndrome Type 1B, autosomal dominant neovascular inflammatory vitreoretinopathy, familial exudative vitreoretinopathy, and Best's macular dystrophy. For a review of the macular dystrophies, see Sullivan & Daiger, 1996, Mol. Med. Today 2:380-386.

Cone-rod dystrophies involve an initial loss of cone photoreceptors followed by the degeneration of rod photoreceptors. This loss of photoreceptors can lead to blindness. Cone-rod dystrophies appear to be a heterogeneous group of inherited disorders for which multiple chromosomal locations have been implicated (Evans et al., 1994, Nature Genet. 6:210-213; Kelsell et al., 1997, Hum. Mol. Genet. 6:597-600). In particular, Kelsell et al., 1998, Am. J. Hum. Genet. 63:274-279 found a candidate gene (CORD7) located at chromosome 6q in a four-generation British family affected with cone-rod dystrophy. A marker in 6q, D6S280, showed a high LOD score of 3.31 (at genetic distance = 0).

Stargardt-like macular dystrophy is an inherited, dominant retinal disease. Affected individuals have normal vision in early childhood but show impaired central vision either in late childhood or early adulthood. The first observable characteristics of the disease are flecks seen in the macula. This is followed by central atrophy, resulting in visual acuity decreasing to 20/200 or worse (Stone et al., Arch. Ophthalmol. 112:765-772 [Stone]). Stone mapped a gene responsible for Stargardt-like macular dystrophy to chromosome 6q. The marker D6S280 was observed by Stone to have the high LOD score of 5.5 (at genetic distance = 0).

Cone-rod dystrophy and Stargardt-like macular dystrophy appear different from a clinical perspective. For example, Stargardt-like macular dystrophy

generally begins in childhood and involves white/yellow flecks in the retina while cone-rod dystrophy is an adult-onset disorder in which no flecks are present. Despite such clinical differences, both diseases may be caused by mutations in the same gene. It is not uncommon for different mutations in a single gene to give rise to clinically different disorders. For example, depending upon the particular mutation, mutations in the peripherin/RDS gene can give rise to either butterfly-shaped pigment dystrophy of the fovea, retinitis pigmentosa, pattern dystrophy, flavus maculatus, macular dystrophy, or central areolar choroidal dystrophy (Nichols et al., 1993, *Nature Genet.* 3:202-207; Weleber et al., 1993, *Arch. Ophthalmol.* 111:1531-1542; Wells et al., 1993, *Nature Genet.* 3:213-218; Reig et al., 1995, *Ophthalmic. Genet.* 16:39-44).

While studies of macular dystrophies such as cone-rod dystrophy or Stargardt-like macular dystrophy are valuable in themselves, such studies are also valuable in that they are expected to shed light on age-related macular degeneration (AMD). AMD is the leading cause of severe visual loss in older individuals. Genetic factors apparently play a role in AMD (Hyman et al., 1983, *Am. J. Epidemiol.* 118:213-227; Gass, 1973, *Arch. Ophthalmol.* 90:206-217). It is believed likely that mild allelic variations of such earlier-onset diseases as cone-rod dystrophy and Stargardt-like macular dystrophy are responsible for some cases of AMD. Thus, understanding and developing treatments for these earlier-onset diseases should prove valuable with respect to AMD as well.

Salla disease is a recessive condition characterized by early-onset psychomotor retardation and ataxia that involves defects in the lysosomal transport of sialic acid. Leppänen et al., 1996, *Genomics* 37:62-67 (Leppänen) located the gene for Salla disease in the immediate vicinity of the marker D6S280. Leppänen screened a PAC library with the marker D6S280 and obtained three positive clones, among which were PAC 141B1 and PAC 224H23, strongly suggesting that the gene for Salla disease is present on these PACs.

SUMMARY OF THE INVENTION

The present invention is directed to novel human DNA sequences encoding a voltage-gated potassium channel, KCNQ5, located in a chromosomal region that contains a gene associated with Stargardt-like macular dystrophy, cone-rod macular dystrophy, and Salla disease.

The present invention includes genomic KCNQ5 DNA as well as cDNA that encodes the KCNQ5 protein. The human genomic KCNQ5 DNA is substantially free from other nucleic acids and has the nucleotide sequence shown in SEQ.ID.NO.:1. The human cDNA encoding KCNQ5 protein is substantially free
5 from other nucleic acids and has the nucleotide sequence shown in SEQ.ID.NO.:2. Also provided is KCNQ5 protein encoded by the novel DNA sequences. The human KCNQ5 protein is substantially free from other proteins and has the amino acid sequence shown in SEQ.ID.NO.:3. Methods of expressing KCNQ5 protein in recombinant systems are provided as well as methods of identifying activators and
10 inhibitors of KCNQ5 protein function. Also provided are diagnostic methods that detect carriers of mutant KCNQ5 genes.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A-AO shows the genomic DNA sequence of human KCNQ5
15 (SEQ.ID.NO.:1). Underlined nucleotides in capitals represent exons. The start ATG codon in exon 1 and the stop TAA codon in exon 14 are shown in bold italics. The D6D280 genetic marker and a phosphoglycerate pseudogene are underlined in bold. The exact lengths of the gaps between exons 1 and 2, 2 and 3, 10 and 11, 11 and 12, 12 and 13, and 13 and 14 are unknown. These gaps are represented as runs of ten
20 bold ns for the sake of convenience.

Figure 2A-E shows the nucleotide sequence (SEQ.ID.NO.:2) and encoded amino acid sequence (SEQ.ID.NO.:3) of human KCNQ5 cDNA. The ATG start codon is at position 138; the TAA stop codon is at position 2,676.

Figure 3A shows the results of a Northern blot of KCNQ5 mRNA
25 expression in various human tissues. Figure 3B shows the results of RT-PCR analysis of KCNQ5 mRNA expression in various human tissues.

Figure 4A shows a sequence alignment of human KCNQ5 protein
(SEQ.ID.NO.:3) with human KCNQ4 protein (SEQ.ID.NO.:4). The consensus sequence shown is (SEQ.ID.NO.:5). Figure 4B-C shows a multiple sequence
30 alignment between human KCNQ5 protein (SEQ.ID.NO.:3), human KCNQ1 protein (SEQ.ID.NO.:43), human KCNQ2 protein (SEQ.ID.NO.:6), human KCNQ3 protein (SEQ.ID.NO.:7), and human KCNQ4 protein (SEQ.ID.NO.:4). The consensus sequence shown is (SEQ.ID.NO.:8).

DETAILED DESCRIPTION OF THE INVENTION

For the purposes of this invention:

"Substantially free from other proteins" means at least 90%, preferably 95%, more preferably 99%, and even more preferably 99.9%, free of other proteins.

- 5 Thus, a KCNQ5 protein preparation that is substantially free from other proteins will contain, as a percent of its total protein, no more than 10%, preferably no more than 5%, more preferably no more than 1%, and even more preferably no more than 0.1%, of non- KCNQ5 proteins. Whether a given KCNQ5 protein preparation is substantially free from other proteins can be determined by such conventional techniques of assessing protein purity as, *e.g.*, sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) combined with appropriate detection methods, *e.g.*, silver staining or immunoblotting.

- 10 "Substantially free from other nucleic acids" means at least 90%, preferably 95%, more preferably 99%, and even more preferably 99.9%, free of other nucleic acids. Thus, a KCNQ5 DNA preparation that is substantially free from other nucleic acids will contain, as a percent of its total nucleic acid, no more than 10%, preferably no more than 5%, more preferably no more than 1%, and even more preferably no more than 0.1%, of non- KCNQ5 nucleic acids. Whether a given KCNQ5 DNA preparation is substantially free from other nucleic acids can be determined by such conventional techniques of assessing nucleic acid purity as, *e.g.*, agarose gel electrophoresis combined with appropriate staining methods, *e.g.*, ethidium bromide staining, or by sequencing.

- 20 A "conservative amino acid substitution" refers to the replacement of one amino acid residue by another, chemically similar, amino acid residue. Examples of such conservative substitutions are: substitution of one hydrophobic residue (isoleucine, leucine, valine, or methionine) for another; substitution of one polar residue for another polar residue of the same charge (*e.g.*, arginine for lysine; glutamic acid for aspartic acid); substitution of one aromatic amino acid (tryptophan, tyrosine, or phenylalanine) for another.

- 30 A polypeptide has "substantially the same biological activity as KCNQ5" if that polypeptide conducts a voltage-gated potassium current when expressed in appropriate cell types and has an amino acid sequence that is at least about 50% identical to SEQ.ID.NO.:3 when measured by such standard programs as BLAST or FASTA.

The present invention relates to the identification and cloning of KCNQ5, a gene encoding a novel voltage-gated potassium channel. The human KCNQ5 gene is located on chromosome 6q14, in a chromosomal region that contains genes that have been linked with the occurrence of at least three diseases: Stargardt-like macular dystrophy, cone-rod dystrophy, and Salla disease.

The human KCNQ5 gene is present on PAC clones from chromosomal region 6q14. PAC141B1 was sequenced and KCNQ5 was found based on homology between the genomic sequences of KCNQ5 present in PAC 141B1 and the sequences of known potassium channel genes. PAC 141B1 is available from Research Genetics, Inc., Huntsville, AL, as an individual clone from the RPCI4,5,6 Library (catalog number CTLIC). Using PCR primers derived from the KCNQ5 sequence, a cDNA sequence representing the coding region as well as a large portion of the 3'-UTR of KCNQ5 was isolated from a human fetal brain cDNA library. Comparison of this cDNA clone with the genomic sequences present in PAC141B1, as well as KCNQ5 sequences found in PAC224H23, showed that exons 3-11 and portions of flanking intronic regions are present in PAC141B1. Exon 2 and flanking intronic regions were found in PAC224H23, while the rest of the KCNQ5 gene (exons 1, 12-14, and flanking intronic regions) was recovered from total human genomic DNA by using cDNA primers and a GenomeWalker kit from Clontech, Palo Alto, CA.

PAC141B1 and PAC224H23 are located in the region of the Salla disease gene (Leppänen et al., 1996, Genomics 37:62-67). PAC141B1 contains the polymorphic genetic marker D6S280 that is located in intron 3 of the KCNQ5 gene between exons 3 and 4 (Figure 1). D6S280 is the marker that detects the maximum LOD score of 5.5 (at genetic distance = 0) in families with Stargardt-like macular dystrophy (Stone et al., Arch. Ophthalmol. 112:765-772). D6S280 also detects a LOD score of 3.31 (at genetic distance = 0) in families with cone-rod dystrophy (Kelsell et al., 1998, Am. J. Hum. Genet. 63:274-279). These LOD scores indicate that D6S280 is very closely linked to, and probably is within, the gene for Stargardt-like macular dystrophy and cone-rod dystrophy. In view of these findings, it is likely that KCNQ5 is involved in Salla disease, Stargardt-like macular dystrophy, and cone-rod dystrophy.

That KCNQ5 should be involved with these three diseases is consistent with its expression pattern (see Figure 3A-B) which shows that KCNQ5 is expressed predominately in the retina and brain, in addition to being expressed in the

skeletal muscle. Stargardt-like macular dystrophy and cone-rod dystrophy are inherited retinal diseases while Salla disease is a disorder that is characterized by early onset psychomotor retardation and ataxia.

Bioinformatic analysis revealed a striking homology of the KCNQ5 protein to a group of voltage gated potassium channels (KCNQ1, KCNQ2, KCNQ3, and KCNQ4; see Figure 4A-B). All of the typical amino acid motifs of these potassium channels are preserved in KCNQ5. A Kyte-Doolittle algorithm analysis predicts a transmembrane organization for KCNQ5 that is typical for this group of potassium channels. Mutations in members of this family of potassium channels have been shown to result in inherited disease (KCNQ2 and KCNQ3, epilepsy [Biervert et al., 1998, Science 279:403-406; Singh et al., 1998, Nature Genet. 18:25-29; Schroeder et al., Nature 1998, 396:687-690]; KCNQ4, a form of nonsyndromic dominant deafness [Kubisch et al., 1999, Cell 96:437-446], KCNQ1, congenital long QT syndrome which causes cardiac arrhythmias and sudden death [Splawski et al., 1997, N. Engl. J. Med. 336:1562-1567]).

The present invention provides DNA encoding KCNQ5 that is substantially free from other nucleic acids. The present invention also provides recombinant DNA molecules encoding KCNQ5. The present invention provides DNA molecules substantially free from other nucleic acids comprising the nucleotide sequence shown in Figure 1 as SEQ.ID.NO.:1. Analysis of SEQ.ID.NO.:1 revealed that this genomic sequence defines a gene having 14 exons. These exons collectively have an open reading frame that encodes a protein of 846 amino acids.

The present invention includes cDNA encoding KCNQ5 protein. Such a cDNA is shown in Figure 2 as SEQ.ID.NO.:2. The present invention therefore includes DNA comprising the nucleotide sequence SEQ.ID.NO.:2. The DNA can be isolated or substantially free of other DNA sequences.

The present invention includes DNA molecules substantially free from other nucleic acids comprising the coding region of SEQ.ID.NO.:2. Accordingly, the present invention includes DNA molecules substantially free from other nucleic acids having a sequence comprising positions 138-2,675 of SEQ.ID.NO.:2. Also included are recombinant DNA molecules having a nucleotide sequence comprising positions 138-2,675 of SEQ.ID.NO.:2 and isolated DNA molecules having a nucleotide sequence comprising positions 138-2,675 of SEQ.ID.NO.:2.

The novel DNA sequences of the present invention encoding KCNQ5, in whole or in part, can be linked with other DNA sequences, *i.e.*, DNA sequences to which KCNQ5 is not naturally linked, to form "recombinant DNA molecules" encoding KCNQ5. Such other sequences can include DNA sequences that control transcription or translation such as, *e.g.*, translation initiation sequences, promoters for RNA polymerase II, transcription or translation termination sequences, enhancer sequences, sequences that control replication in microorganisms, sequences that confer antibiotic resistance, or sequences that encode a polypeptide "tag" such as, *e.g.*, a polyhistidine tract or the myc epitope. The novel DNA sequences of the present invention can be inserted into vectors such as plasmids, cosmids, viral vectors, P1 artificial chromosomes, or yeast artificial chromosomes.

Included in the present invention are DNA sequences that hybridize to at least one of SEQ.ID.NO:1 or SEQ.ID.NO:2 under stringent conditions. By way of example, and not limitation, a procedure using conditions of high stringency is as follows: Prehybridization of filters containing DNA is carried out for 2 hr. to overnight at 65°C in buffer composed of 6X SSC, 5X Denhardt's solution, and 100 µg/ml denatured salmon sperm DNA. Filters are hybridized for 12 to 48 hrs at 65°C in prehybridization mixture containing 100 µg/ml denatured salmon sperm DNA and 5-20 X 10⁶ cpm of ³²P-labeled probe. Washing of filters is done at 37°C for 1 hr in a solution containing 2X SSC, 0.1% SDS. This is followed by a wash in 0.1X SSC, 0.1% SDS at 50°C for 45 min. before autoradiography.

Other procedures using conditions of high stringency would include either a hybridization carried out in 5XSSC, 5X Denhardt's solution, 50% formamide at 42°C for 12 to 48 hours or a washing step carried out in 0.2X SSPE, 0.2% SDS at 65°C for 30 to 60 minutes.

Reagents mentioned in the foregoing procedures for carrying out high stringency hybridization are well known in the art. Details of the composition of these reagents can be found in, *e.g.*, Sambrook, Fritsch, and Maniatis, 1989, Molecular Cloning: A Laboratory Manual, second edition, Cold Spring Harbor Laboratory Press. In addition to the foregoing, other conditions of high stringency which may be used are well known in the art.

The degeneracy of the genetic code is such that, for all but two amino acids, more than a single codon encodes a particular amino acid. This allows for the construction of synthetic DNA that encodes the KCNQ5 protein where the nucleotide

sequence of the synthetic DNA differs significantly from the nucleotide sequences of SEQ.ID.NO:2, but still encodes the same KCNQ5 protein as SEQ.ID.NO:2. Such synthetic DNAs are intended to be within the scope of the present invention.

- Mutated forms of SEQ.ID.NO:1 or SEQ.ID.NO:2 are intended to be
- 5 within the scope of the present invention. In particular, mutated forms of SEQ.ID.NO:1 or SEQ.ID.NO:2 which give rise to Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration are within the scope of the present invention.

- Another aspect of the present invention includes host cells that have
- 10 been engineered to contain and/or express DNA sequences encoding KCNQ5 protein. Such recombinant host cells can be cultured under suitable conditions to produce KCNQ5 protein. An expression vector containing DNA encoding KCNQ5 protein can be used for expression of KCNQ5 protein in a recombinant host cell. Recombinant host cells may be prokaryotic or eukaryotic, including but not limited to,
- 15 bacteria such as *E. coli*, fungal cells such as yeast, mammalian cells including, but not limited to, cell lines of human, bovine, porcine, monkey and rodent origin, amphibian cells such as *Xenopus* oocytes, and insect cells including but not limited to *Drosophila* and silkworm derived cell lines. Cells and cell lines which are suitable for recombinant expression of KCNQ5 protein and which are widely mavailable,
- 20 include but are not limited to, L cells L-M(TK⁻) (ATCC CCL 1.3), L cells L-M (ATCC CCL 1.2), 293 (ATCC CRL 1573), Raji (ATCC CCL 86), CV-1 (ATCC CCL 70), COS-1 (ATCC CRL 1650), COS-7 (ATCC CRL 1651), CHO-K1 (ATCC CCL 61), 3T3 (ATCC CCL 92), NIH/3T3 (ATCC CRL 1658), HeLa (ATCC CCL 2), C127I (ATCC CRL 1616), BS-C-1 (ATCC CCL 26), MRC-5 (ATCC CCL 171),
- 25 ARPE-19 human retinal pigment epithelium (ATCC CRL-2302), *Xenopus* melanophores, and *Xenopus* oocytes.

- A variety of mammalian expression vectors can be used to express recombinant KCNQ5 in mammalian cells. Commercially available mammalian expression vectors which are suitable include, but are not limited to, pMC1neo
- 30 (Stratagene), pSG5 (Stratagene), pcDNAI and pcDNAIamp, pcDNA3, pcDNA3.1, pCR3.1 (Invitrogen), EBO-pSV2-neo (ATCC 37593), pBPV-1(8-2) (ATCC 37110), pdBPV-MMTneo(342-12) (ATCC 37224), pRSVgpt (ATCC 37199), pRSVneo (ATCC 37198), and pSV2-dhfr (ATCC 37146). Another suitable vector is the PT7TS oocyte expression vector. Following expression in recombinant cells, KCNQ5 can

be purified by conventional techniques to a level that is substantially free from other proteins.

Certain voltage-gated potassium channel subunits have been found to require the expression of other voltage-gated potassium channel subunits as "chaperones" in order to be properly expressed at high levels and inserted in membranes. For example, co-expression of KCNQ3 appears to enhance the expression of KCNQ2 in *Xenopus* oocytes (Wang et al., 1998, Science 282:1890-1893). Also, some voltage-gated potassium channel Kv1 α subunits require other related alpha subunits or Kv β 2 subunits (Shi et al., 1995, Neuron 16:843-852). Accordingly, the recombinant expression of the KCNQ5 protein may under certain circumstances benefit from the co-expression of other voltage-gated potassium channel proteins and such co-expression is intended to be within the scope of the present invention.

The present invention includes KCNQ5 protein substantially free from other proteins. The amino acid sequence of the full-length KCNQ5 protein is shown in Figure 2 as SEQ.ID.NO.:3. Thus, the present invention includes KCNQ5 protein substantially free from other proteins having the amino acid sequence SEQ.ID.NO.:3. The present invention also includes isolated KCNQ5 protein having the amino acid sequence SEQ.ID.NO.:3.

Mutated forms of KCNQ5 proteins are intended to be within the scope of the present invention. In particular, mutated forms of SEQ.ID.NO.:3 that give rise to Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration are within the scope of the present invention.

As with many proteins, it is possible to modify many of the amino acids of KCNQ5 and still retain substantially the same biological activity as the original protein. Thus, the present invention includes modified KCNQ5 proteins which have amino acid deletions, additions, or substitutions but that still retain substantially the same biological activity as KCNQ5. It is generally accepted that single amino acid substitutions do not usually alter the biological activity of a protein (see, e.g., Molecular Biology of the Gene, Watson et al., 1987, Fourth Ed., The Benjamin/Cummings Publishing Co., Inc., page 226; and Cunningham & Wells, 1989, Science 244:1081-1085). Accordingly, the present invention includes polypeptides where one amino acid substitution has been made in SEQ.ID.NO.:3 wherein the polypeptides still retain substantially the same biological activity as

KCNQ5. The present invention also includes polypeptides where two or more amino acid substitutions have been made in SEQ.ID.NO:3 wherein the polypeptides still retain substantially the same biological activity as KCNQ5. In particular, the present invention includes embodiments where the above-described substitutions are

5 conservative substitutions. In particular, the present invention includes embodiments where the above-described substitutions do not occur in positions where the amino acid present in KCNQ5 is also present in the corresponding position of any one of KCNQ1, KCNQ2, KCNQ3, or KCNQ4 (see Figure 4A-B).

The KCNQ5 proteins of the present invention may contain post-

10 translational modifications, *e.g.*, covalently linked carbohydrate, phosphorylation, myristoylation, *etc.*.

The present invention also includes chimeric KCNQ5 proteins. Chimeric KCNQ5 proteins consist of a contiguous polypeptide sequence of at least a portion of KCNQ5 protein fused to a polypeptide sequence of a non-KCNQ5 protein.

15 The present invention also includes isolated forms of KCNQ5 proteins and KCNQ5 DNA. Use of the term "isolated" indicates that KCNQ5 protein or KCNQ5 DNA has been removed from its normal cellular environment. Thus, an isolated KCNQ5 protein may be in a cell-free solution or placed in a different cellular environment from that in which it occurs naturally. The term isolated does not imply

20 that an isolated KCNQ5 protein is the only protein present, but instead means that an isolated KCNQ5 protein is at least 95% free of non-amino acid material (*e.g.*, nucleic acids, lipids, carbohydrates) naturally associated with the KCNQ5 protein. Thus, a KCNQ5 protein that is expressed in bacteria or even in eukaryotic cells which do not naturally (*i.e.*, without human intervention) express it through recombinant means is

25 an "isolated KCNQ5 protein."

It is known that other members of the family of potassium channels to which KCNQ5 belongs can interact to form heteromeric structures resulting in functional potassium channels. For example, KCNQ2 and KCNQ3 can assemble to form a heteromeric functional potassium channel (Wang et al., 1998, Science

30 282:1890-1893). Accordingly, it is believed likely that KCNQ5 will also be able to form heteromeric structures with other proteins where such heteromeric structures constitute functional potassium channels. Thus, the present invention includes such heteromers comprising KCNQ5. Preferred heteromers are those in which KCNQ5 forms heteromers with at least one of KCNQ1, KCNQ2, KCNQ3, or KCNQ4.

A cDNA fragment encoding full-length KCNQ5 can be isolated from a human retinal or brain cDNA library by using the polymerase chain reaction (PCR) employing suitable primer pairs. Such primer pairs can be selected based upon the cDNA sequence for KCNQ5 shown in Figure 2 as SEQ.ID.NO.:2. Suitable primer

5 pairs would be, e.g.:

5'-GGGGGCCCCGGATGAGCC-3' (SEQ.ID.NO.:9) and

5'-GAAGAACTTATTTTCAGTTTGA-3' (SEQ.ID.NO.:10)

The above primers are meant to be illustrative only; one skilled in the art would readily be able to design other suitable primers based upon SEQ.ID.NO.:2.

10 Such primers could be produced by methods of oligonucleotide synthesis that are well known in the art.

PCR reactions can be carried out with a variety of thermostable enzymes including but not limited to AmpliTaq, AmpliTaq Gold, or Vent polymerase. For AmpliTaq, reactions can be carried out in 10 mM Tris-Cl, pH 8.3, 2.0 mM

15 MgCl₂, 200 μ M for each dNTP, 50 mM KCl, 0.2 μ M for each primer, 10 ng of DNA template, 0.05 units/ μ l of AmpliTaq. The reactions are heated at 95°C for 3 minutes and then cycled 35 times using the cycling parameters of 95°C, 20 seconds, 62°C, 20 seconds, 72°C, 3 minutes. In addition to these conditions, a variety of suitable PCR protocols can be found in PCR Primer, A Laboratory Manual, edited by C.W.

20 Dieffenbach and G.S. Dveksler, 1995, Cold Spring Harbor Laboratory Press; or PCR Protocols: A Guide to Methods and Applications, Michael *et al.*, eds., 1990, Academic Press.

A suitable cDNA library from which a clone encoding KCNQ5 can be isolated would be Human Retina 5'-stretch cDNA library in lambda gt10 or lambda

25 gt11 vectors (catalog numbers HL1143a and HL1132b, Clontech, Palo Alto, CA) or human fetal brain 5'-stretch plus cDNA library (catalog number HL5024t, Clontech, Palo Alto, CA). The primary clones of such a library can be subdivided into pools with each pool containing approximately 20,000 clones and each pool can be amplified separately.

30 By this method, a cDNA fragment encoding an open reading frame of 846 amino acids (SEQ.ID.NO.:3) can be obtained. This cDNA fragment can be cloned into a suitable cloning vector or expression vector. For example, the fragment can be cloned into the mammalian expression vector pcDNA3.1 (Invitrogen, San Diego, CA). KCNQ5 protein can then be produced by transferring an expression

vector encoding KCNQ5 or portions thereof into a suitable host cell and growing the host cell under appropriate conditions. KCNQ5 protein can then be isolated by methods well known in the art.

- As an alternative to the above-described PCR method, a cDNA clone encoding KCNQ5 can be isolated from a cDNA library using as a probe oligonucleotides specific for KCNQ5 and methods well known in the art for screening cDNA libraries with oligonucleotide probes. Such methods are described in, *e.g.*, Sambrook *et al.*, 1989, *Molecular Cloning: A Laboratory Manual*; Cold Spring Harbor Laboratory, Cold Spring Harbor, New York; Glover, D.M. (ed.), 1985, *DNA Cloning: A Practical Approach*, MRL Press, Ltd., Oxford, U.K., Vol. I, II.
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- Oligonucleotides that are specific for KCNQ5 and that can be used to screen cDNA libraries can be readily designed based upon the cDNA sequence of KCNQ5 shown in Figure 2 as SEQ.ID.NO.:2 and can be synthesized by methods well-known in the art.
- Genomic clones containing the KCNQ5 gene can be obtained from commercially available human PAC or BAC libraries available from Research Genetics, Huntsville, AL. PAC clones containing the KCNQ5 gene (*e.g.*, PAC141B1, PAC224H23) are commercially available from Research Genetics, Huntsville, AL (catalog number for individual PAC clones is RPC1.C). Alternatively, one may prepare genomic libraries, especially in P1 artificial chromosome vectors, from which genomic clones containing the KCNQ5 can be isolated, using probes based upon the KCNQ5 sequences disclosed herein. Methods of preparing such libraries are known in the art (Ioannou *et al.*, 1994, *Nature Genet.* 6:84-89).

- The novel DNA sequences of the present invention can be used in various diagnostic methods relating to Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration. The present invention provides diagnostic methods for determining whether a patient carries a mutation in the KCNQ5 gene that predisposes that patient toward the development of Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration. In broad terms, such methods comprise determining the DNA sequence of a region of the KCNQ5 gene from the patient and comparing that sequence to the sequence from the corresponding region of the KCNQ5 gene from a non-affected person, *i.e.*, a person who does not suffer from Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration, where a difference in sequence between the DNA sequence of the KCNQ5 gene from the
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patient and the DNA sequence of the KCNQ5 gene from the non-affected person indicates that the patient has Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration.

Such methods of diagnosis may be carried out in a variety of ways.

5 For example, one embodiment comprises:

- (a) providing PCR primers from a region of the KCNQ5 gene;
 - (b) performing PCR on a DNA sample from the patient to produce a PCR fragment from the patient;
 - (c) performing PCR on a control DNA sample comprising a nucleotide sequence selected from the group consisting of SEQ.ID.NO:1 and SEQ.ID.NO:2 to produce a control PCR fragment;
 - (d) determining the nucleotide sequence of the PCR fragment from the patient and the nucleotide sequence of the control PCR fragment;
 - (e) comparing the nucleotide sequence of the PCR fragment from the patient to the nucleotide sequence of the control PCR fragment;
- 15 where a difference between the nucleotide sequence of the PCR fragment from the patient and the nucleotide sequence of the control PCR fragment indicates that the patient has a mutation in the KCNQ5 gene and thus is likely to have Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration.
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In a particular embodiment, the PCR primers are from a region of the KCNQ5 gene where it is suspected that a patient harbors a mutation. In a particular embodiment, the PCR primers are from the coding region of the KCNQ5 gene, *i.e.*, from the coding region of SEQ.ID.NO:1 or SEQ.ID.NO:2. In a particular

25 embodiment, the PCR primers amplify a region that includes the marker D6S280.

In a particular embodiment, the DNA sample from the patient is cDNA that has been prepared from an RNA sample from the patient. In another embodiment, the DNA sample from the patient is genomic DNA. In a particular embodiment, the control DNA sample is DNA from a person who does not have

30 Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration.

In a particular embodiment, the nucleotide sequences of the PCR fragment from the patient and the control PCR fragment are determined by DNA sequencing.

In a particular embodiment, the nucleotide sequences of the PCR fragment from the patient and the control PCR fragment are compared by direct comparison after DNA sequencing. In another embodiment, step (d) is omitted and the comparison in step (e) is made by a process that includes hybridizing the PCR fragment from the patient and the control PCR fragment and then using an endonuclease that cleaves at any mismatched positions in the hybrid but does not cleave the hybrid if the two fragments match perfectly. Such an endonuclease is, e.g., S1. In this embodiment, the conversion of the PCR fragment from the patient to smaller fragments after endonuclease treatment indicates that the patient carries a mutation in the KCNQ5 gene. In such embodiments, it may be advantageous to label (radioactively, enzymatically, immunologically, *etc.*) the PCR fragment from the patient or the control PCR fragment.

The present invention provides a method of diagnosing whether a patient carries a mutation in the KCNQ5 gene that comprises:

- 15 (a) obtaining an RNA sample from the patient;
- (b) performing reverse transcription-PCR (RT-PCR) on the RNA sample using primers that span a region of the coding sequence of the KCNQ5 gene to produce a PCR fragment from the patient where the PCR fragment from the patient has a defined length, the length being dependent upon the identity of the primers that
20 were used in the RT-PCR;
- (c) hybridizing the PCR fragment to DNA comprising a sequence selected from the group consisting of SEQ.ID.NO.:1 and SEQ.ID.NO.:2, or to portions of SEQ.ID.NO.:1 or SEQ.ID.NO.:2 that are sufficiently long to give rise to bands that can be seen on polyacrylamide gels, to form a hybrid;
- 25 (d) treating the hybrid produced in step (c) with an endonuclease that cleaves at any mismatched positions in the hybrid but does not cleave the hybrid if the two fragments match perfectly;
- (e) determining whether the endonuclease cleaved the hybrid by determining the length of the PCR fragment from the patient after endonuclease
30 treatment where a reduction in the length of the PCR fragment from the patient after endonuclease treatment indicates that the patient carries a mutation in the KCNQ5 gene.

In a variation of the above-described method, instead of determining the length of the PCR fragment from the patient after endonuclease treatment, the

length of the DNA comprising a sequence selected from the group consisting of SEQ.ID.NO.:1 and SEQ.ID.NO.:2, or the DNA comprising portions of SEQ.ID.NO.:1 or SEQ.ID.NO.:2 that are sufficiently long to give rise to bands that can be seen on polyacrylamide gels is determined after endonuclease treatment. In such a variation, a
5 reduction in the length of the DNA comprising a sequence selected from the group consisting of SEQ.ID.NO.:1 and SEQ.ID.NO.:2, or the DNA comprising portions of SEQ.ID.NO.:1 or SEQ.ID.NO.:2 that are sufficiently long to give rise to bands that can be seen on polyacrylamide gels indicates that the patient carries a mutation in the KCNQ5 gene.

- 10 The present invention provides a method of diagnosing whether a patient carries a mutation in the KCNQ5 gene that comprises:
- (a) making cDNA from an RNA sample from the patient;
 - (b) providing a set of PCR primers based upon SEQ.ID.NO.:1 or SEQ.ID.NO.:2;
 - 15 (c) performing PCR on the cDNA to produce a PCR fragment from the patient;
 - (d) determining the nucleotide sequence of the PCR fragment from the patient;
 - (e) comparing the nucleotide sequence of the PCR fragment from
20 the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2; where a difference between the nucleotide sequence of the PCR fragment from the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2 indicates that the patient carries a mutation in the KCNQ5 gene.

- The present invention provides a method of diagnosing whether a
25 patient carries a mutation in the KCNQ5 gene that comprises:
- (a) preparing genomic DNA from the patient;
 - (b) providing a set of PCR primers based upon SEQ.ID.NO.:1 or SEQ.ID.NO.:2;
 - (c) performing PCR on the genomic DNA to produce a PCR
30 fragment from the patient;
 - (d) determining the nucleotide sequence of the PCR fragment from the patient;
 - (e) comparing the nucleotide sequence of the PCR fragment from the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2;

where a difference between the nucleotide sequence of the PCR fragment from the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2 indicates that the patient carries a mutation in the KCNQ5 gene.

The present invention also provides oligonucleotide probes, based
5 upon the sequences of SEQ.ID.NO.:1 or SEQ.ID.NO.:2, that can be used in diagnostic methods related to Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration. In particular, the present invention includes DNA oligonucleotides comprising at least about 10, 15, or 18 contiguous
10 nucleotides of a sequence selected from the group consisting of: SEQ.ID.NO.:1 and SEQ.ID.NO.:2 where the oligonucleotide probe comprises no stretch of contiguous nucleotides longer than 5 of a sequence selected from the group consisting of: SEQ.ID.NO.:1 and SEQ.ID.NO.:2 other than the said at least about 10, 15, or 18 contiguous nucleotides. The oligonucleotides can be substantially free from other nucleic acids. Also provided by the present invention are corresponding RNA
15 oligonucleotides. The DNA or RNA oligonucleotide probes can be packaged in kits.

In addition to the diagnostic utilities described above, the present invention makes possible the recombinant expression of the KCNQ5 protein in various cell types. Such recombinant expression makes possible the study of this protein so that its biochemical activity and its role in Stargardt-like macular
20 dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration can be elucidated.

The present invention also makes possible the development of assays which measure the biological activity of the KCNQ5 protein. Such assays using recombinantly expressed KCNQ5 protein are especially of interest. Assays for
25 KCNQ5 protein activity can be used to screen libraries of compounds or other sources of compounds to identify compounds that are activators or inhibitors of the activity of KCNQ5 protein. Such identified compounds can serve as "leads" for the development of pharmaceuticals that can be used to treat patients having Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular
30 degeneration. In versions of the above-described assays, mutant KCNQ5 proteins are used and inhibitors or activators of the activity of the mutant KCNQ5 proteins are identified.

Preferred cell lines for recombinant expression of KCNQ5 are those which do not express endogenous potassium channels (*e.g.*, CV-1, NIH-3T3). Such

cell lines can be loaded with ^{86}Rb , an ion which can pass through potassium channels. The ^{86}Rb -loaded cells can be exposed to collections of substances (*e.g.*, combinatorial libraries, natural products) and those substances that are able to alter ^{86}Rb efflux identified. Such substances are likely to be activators or inhibitors of

5 KCNQ5.

The present invention includes a method of identifying activators or inhibitors of KCNQ5 comprising:

- (a) recombinantly expressing KCNQ5 protein or mutant KCNQ5 protein in a host cell;
- 10 (b) measuring the biological activity of KCNQ5 protein or mutant KCNQ5 protein in the presence and in the absence of a substance suspected of being an activator or an inhibitor of KCNQ5 protein or mutant KCNQ5 protein;

where a change in the biological activity of the KCNQ5 protein or the mutant KCNQ5 protein in the presence as compared to the absence of the substance

15 indicates that the substance is an activator or an inhibitor of KCNQ5 protein or mutant KCNQ5 protein.

In particular embodiments, the biological activity is the production of a voltage-gated potassium current, or efflux of ^{86}Rb .

In particular embodiments, a vector encoding KCNQ5 is transferred

20 into *Xenopus* oocytes in order to cause the expression of KCNQ5 protein in the oocytes. Alternatively, RNA encoding KCNQ5 protein can be prepared *in vitro* and injected into the oocytes, also resulting in the expression of KCNQ5 protein in the oocytes. Following expression of KCNQ5 in the oocytes, membrane currents are measured after the transmembrane voltage is changed in steps. A change in

25 membrane current is observed when the KCNQ5 channels opens, allowing potassium ion flow. Similar oocytes studies were reported for KCNQ2 and KCNQ3 potassium channels in Wang et al., 1998, Science 282:1890-1893.

Inhibitors of KCNQ5 can be identified by exposing the oocytes expressing KCNQ5 to collections of substances and determining whether the

30 substances can block or diminish the membrane currents observed in the absence of the substance.

Accordingly, the present invention provides a method of identifying inhibitors of KCNQ5 comprising:

- (a) expressing KCNQ5 protein in *Xenopus* oocytes;

- (b) changing the transmembrane potential of the oocytes in the presence and the absence of a substance suspected of being an inhibitor of KCNQ5;
- (c) measuring membrane potassium currents following step (b);
- where if the potassium membrane currents measured in step (c) are
- 5 greater in the absence rather than in the presence of the substance, then the substance is an inhibitor of KCNQ5.

The present invention also includes assays for the identification of activators and inhibitors of KCNQ5 that are based upon FRET between a first and a second fluorescent dye where the first dye is bound to one side of the plasma

10 membrane of a cell expressing KCNQ5 and the second dye is free to shuttle from one face of the membrane to the other face in response to changes in membrane potential. In certain embodiments, the first dye is impenetrable to the plasma membrane of the cells and is bound predominately to the extracellular surface of the plasma membrane. The second dye is trapped within the plasma membrane but is free to diffuse within

15 the membrane. At normal (*i.e.*, negative) resting potentials of the membrane, the second dye is bound predominately to the inner surface of the extracellular face of the plasma membrane, thus placing the second dye in close proximity to the first dye. This close proximity allows for the generation of a large amount of FRET between the two dyes. Following membrane depolarization, the second dye moves from the

20 extracellular face of the membrane to the intracellular face, thus increasing the distance between the dyes. This increased distance results in a decrease in FRET, with a corresponding increase in fluorescent emission derived from the first dye and a corresponding decrease in the fluorescent emission from the second dye. See figure 1 of González & Tsien, 1997, Chemistry & Biology 4:269-277. See also González &

25 Tsien, 1995, Biophys. J. 69:1272-1280 and U.S. Patent No. 5,661,035.

In certain embodiments, the first dye is a fluorescent lectin or a fluorescent phospholipid that acts as the fluorescent donor. Examples of such a first dye are: a coumarin-labeled phosphatidylethanolamine (*e.g.*, N-(6-chloro-7-hydroxy-2-oxo-2H--1-benzopyran-3-carboxamidoacetyl)-dimyristoylphosphatidyl-

30 ethanolamine) or N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)-dipalmitoylphosphatidylethanolamine); a fluorescently-labeled lectin (*e.g.*, fluorescein-labeled wheat germ agglutinin). In certain embodiments, the second dye is an oxonol that acts as the fluorescent acceptor. Examples of such a second dye are: bis(1,3-dialkyl-2-thiobarbiturate)trimethineoxonols (*e.g.*, bis(1,3-dihexyl-2-

thiobarbiturate)trimethineoxonol) or pentamethineoxonol analogues (e.g., bis(1,3-dihexyl-2-thiobarbiturate)pentamethineoxonol; or bis(1,3-dibutyl-2-thiobarbiturate)pentamethineoxonol). See González & Tsien, 1997, Chemistry & Biology 4:269-277 for methods of synthesizing various dyes suitable for use in the present invention. In certain embodiments, the assay may comprise a natural carotenoid, e.g., astaxanthin, in order to reduce photodynamic damage due to singlet oxygen.

The above described assays can be utilized to discover activators and inhibitors of KCNQ5. Such assays will generally utilize cells that express KCNQ5, e.g., by transfection with expression vectors encoding KCNQ5. In assays for inhibitors, such cells will generally have a resting membrane potential that is roughly equal to the threshold for activation of the KCNQ5 channel. This is because most untransfected cells will have membrane potentials that are depolarized relative to the threshold potential of KCNQ5 channels. Therefore, when KCNQ5 is expressed in these cells, the KCNQ5 channels open. This lets K⁺ out of the cells, which tends to hyperpolarize the membrane potential. This closes some of the KCNQ5 channels, leading to relative depolarization. In this way, a steady state develops around the threshold for activation of the KCNQ5 channel. Inhibitors of KCNQ5 will, therefore, disturb this steady state and depolarize the cell. In assays for activators, KCNQ5 will be transfected into a cell line that also expresses a counteracting, depolarizing current. The membrane potential in these cells will therefore be set by contributions of both the KCNQ5 channel and the endogenous depolarizing current, resulting in a more depolarized resting potential. Ideally, the endogenous current will play the major role in the absence of a KCNQ5 activator. Activators of KCNQ5 will open this channel and increase the contribution of KCNQ5 to the membrane potential relative to the other current and the potential will, therefore, hyperpolarize in response to an activator of KCNQ5. Changes in membrane potential (depolarizations and hyperpolarizations) that are caused by activators and inhibitors of KCNQ5 can be monitored by the assays using FRET described above.

Accordingly, the present invention provides a method of identifying activators of KCNQ5 comprising:

(a) providing test cells comprising:

(1) an expression vector that directs the expression of KCNQ5 in the cells;

(2) a first fluorescent dye, where the first dye is bound to one side of the plasma membrane; and

(3) a second fluorescent dye, where the second fluorescent dye is free to shuttle from one face of the plasma membrane to the other face in response to changes in membrane potential;

(b) exposing the test cells to a substance that is suspected of being an activator of KCNQ5;

(c) measuring the amount of fluorescence resonance energy transfer (FRET) in the test cells that have been exposed to the substance;

(d) comparing the amount of FRET exhibited by the test cells that have been exposed to the substance with the amount of FRET exhibited by control cells;

wherein if the amount of FRET exhibited by the test cells is greater than the amount of FRET exhibited by the control cells, the substance is an activator of KCNQ5;

where the control cells are either (1) cells that are essentially the same as the test cells except that they do not comprise at least one of the items listed at (a) (1)-(3) but have been exposed to the substance; or (2) test cells that have not been exposed to the substance.

The present invention also provides a method of identifying inhibitors of KCNQ5 comprising:

(a) providing test cells comprising:

(1) an expression vector that directs the expression of KCNQ5 in the cells;

(2) a first fluorescent dye, where the first dye is bound to one side of the plasma membrane; and

(3) a second fluorescent dye, where the second fluorescent dye is free to shuttle from one face of the plasma membrane to the other face in response to changes in membrane potential;

(b) exposing the test cells to a substance that is suspected of being an inhibitor of KCNQ5;

(c) measuring the amount of fluorescence resonance energy transfer (FRET) in the test cells that have been exposed to the substance;

(d) comparing the amount of FRET exhibited by the test cells that have been exposed to the substance with the amount of FRET exhibited by control cells;

wherein if the amount of FRET exhibited by the test cells is less than
5 the amount of FRET exhibited by the control cells, the substance is an inhibitor of KCNQ5;

where the control cells are either (1) cells that are essentially the same as the test cells except that they do not comprise at least one of the items listed at (a) (1)-(3) but have been exposed to the substance; or (2) test cells that have not been
10 exposed to the substance.

In a variation of the assay described above, instead of the transfected cell's membrane potential being allowed to reach steady state on its own, the membrane potential is artificially set at a potential in which the KCNQ5 channel is open. This can be done, *e.g.*, by variation of the external K^+ concentration in a
15 known manner (*e.g.*, increased concentrations of external K^+). If such cells, having open KCNQ5 channels, are exposed to inhibitors of KCNQ5, the KCNQ5 channels will close, and the cells' membrane potentials will be depolarized. This depolarization can be observed as a decrease in FRET.

Accordingly, the present invention provides a method of identifying
20 inhibitors of KCNQ5 comprising:

- (a) providing cells comprising:
 - (1) an expression vector that directs the expression of KCNQ5 in the cells;
 - (2) a first fluorescent dye, where the first dye is bound to
25 one side of the plasma membrane; and
 - (3) a second fluorescent dye, where the second fluorescent dye is free to shuttle from one face of the plasma membrane to the other face in response to changes in membrane potential;
- (b) adjusting the membrane potential of the cells such that the ion
30 channel formed by KCNQ5 is open;
- (c) measuring the amount of fluorescence resonance energy transfer (FRET) in the test cells;
- (d) repeating step (b) and step (c) while the cells are exposed to a substance that is suspected of being an inhibitor of KCNQ5;

where if the amount of FRET exhibited by the cells that are exposed to the substance is less than the amount of FRET exhibited by the cells that have not been exposed to the substance, then the substance is an inhibitor of KCNQ5.

In particular embodiments of the above-described methods, the
5 expression vectors are transfected into the test cells.

In particular embodiments of the above-described methods, KCNQ5 has an amino acid sequence of SEQ.ID.NO.:3.

In particular embodiments of the above-described methods, the first
10 fluorescent dye is selected from the group consisting of: a fluorescent lectin; a fluorescent phospholipid; a coumarin-labeled phosphatidylethanolamine; N-(6-chloro-7-hydroxy-2-oxo-2H--1-benzopyran-3-carboxamidoacetyl)-dimyristoylphosphatidylethanolamine); N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)-dipalmitoylphosphatidylethanolamine); and fluorescein-labeled wheat germ agglutinin.

15 In particular embodiments of the above-described methods, the second fluorescent dye is selected from the group consisting of: an oxonol that acts as the fluorescent acceptor; bis(1,3-dialkyl-2-thiobarbiturate)trimethineoxonols; bis(1,3-dihexyl-2-thiobarbiturate)trimethineoxonol; bis(1,3-dialkyl-2-thiobarbiturate)quatramethineoxonols; bis(1,3-dialkyl-2-
20 thiobarbiturate)pentamethineoxonols; bis(1,3-dihexyl-2-thiobarbiturate)pentamethineoxonol; bis(1,3-dibutyl-2-thiobarbiturate)pentamethineoxonol); and bis(1,3-dialkyl-2-thiobarbiturate)hexamethineoxonols.

In a particular embodiment of the above-described methods, the cells
25 are eukaryotic cells. In another embodiment, the cells are mammalian cells. In other embodiments, the cells are L cells L-M(TK⁻) (ATCC CCL 1.3), L cells L-M (ATCC CCL 1.2), 293 (ATCC CRL 1573), Raji (ATCC CCL 86), CV-1 (ATCC CCL 70), COS-1 (ATCC CRL 1650), COS-7 (ATCC CRL 1651), CHO-K1 (ATCC CCL 61), 3T3 (ATCC CCL 92), NIH/3T3 (ATCC CRL 1658), HeLa (ATCC CCL 2), C127I
30 (ATCC CRL 1616), BS-C-1 (ATCC CCL 26), MRC-5 (ATCC CCL 171), *Xenopus* melanophores, or *Xenopus* oocytes.

In particular embodiments of the above-described methods, the control cells do not comprise item (a)(1) but do comprise items (a)(2) and (a)(3).

In assays to identify activators or inhibitors of KCNQ5, it may be advantageous to co-express another potassium channel, *e.g.*, KCNQ1, KCNQ2, KCNQ3, or KCNQ4, together with KCNQ5, or with an accessory subunit, such as the Isk protein or one of its homologues, in order to form a functional heteromeric potassium channel.

While the above-described methods are explicitly directed to testing whether "a" substance is an activator or inhibitor of KCNQ5, it will be clear to one skilled in the art that such methods can be adapted to test collections of substances, *e.g.*, combinatorial libraries, to determine whether any members of such collections are activators or inhibitors of KCNQ5. Accordingly, the use of collections of substances, or individual members of such collections, as the substance in the above-described methods is within the scope of the present invention.

The present invention includes pharmaceutical compositions comprising activators or inhibitors of KCNQ5 protein that have been identified by the herein-described methods. The activators or inhibitors are generally combined with pharmaceutically acceptable carriers to form pharmaceutical compositions. Examples of such carriers and methods of formulation of pharmaceutical compositions containing activators or inhibitors and carriers can be found in Remington's Pharmaceutical Sciences. To form a pharmaceutically acceptable composition suitable for effective administration, such compositions will contain a therapeutically effective amount of the activators or inhibitors.

Therapeutic or prophylactic compositions are administered to an individual in amounts sufficient to treat or prevent conditions where KCNQ5 activity is abnormal. The effective amount can vary according to a variety of factors such as the individual's condition, weight, gender, and age. Other factors include the mode of administration. The appropriate amount can be determined by a skilled physician.

Compositions can be used alone at appropriate dosages. Alternatively, co-administration or sequential administration of other agents can be desirable.

The compositions can be administered in a wide variety of therapeutic dosage forms in conventional vehicles for administration. For example, the compositions can be administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixirs, tinctures, solutions, suspensions, syrups and emulsions, or by injection. Likewise, they can also be administered in intravenous (both bolus and infusion),

intraperitoneal, subcutaneous, topical with or without occlusion, or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts.

Advantageously, compositions can be administered in a single daily dose, or the total daily dosage can be administered in divided doses of two, three or
5 four times daily. Furthermore, compositions can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the
10 dosage regimen.

The dosage regimen utilizing the compositions is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal, hepatic and cardiovascular function of the patient; and
15 the particular composition thereof employed. A physician of ordinary skill can readily determine and prescribe the effective amount of the composition required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentrations of composition within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the composition's availability to
20 target sites. This involves a consideration of the distribution, equilibrium, and elimination of a composition.

The present invention includes a method of treating Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, age-related macular degeneration and other forms of macular degeneration, deafness, epilepsy, and
25 different forms of neuropsychiatric, heart, gastrointestinal, and muscle disorders by administering to a patient a therapeutically effective amount of a substance that is an activator or an inhibitor of a voltage-gated potassium channel containing the KCNQ5 protein.

When screening compounds in order to identify potential
30 pharmaceuticals that specifically interact with a target ion channel, it is necessary to ensure that the compounds identified are as specific as possible for the target ion channel. To do this, it is necessary to screen the compounds against as wide an array as possible of ion channels that are similar to the target ion channel. Thus, in order to find compounds that are potential pharmaceuticals that interact with ion channel A, it

is not enough to ensure that the compounds interact with ion channel A (the "plus target") and produce the desired pharmacological effect through ion channel A. It is also necessary to determine that the compounds do not interact with ion channels B, C, D, *etc.* (the "minus targets"). In general, as part of a screening program, it is important to have as many minus targets as possible (see Hodgson, 1992, Bio/Technology 10:973-980, at 980). KCNQ5 protein, DNA encoding KCNQ5 protein, and recombinant cells that have been engineered to express KCNQ5 protein have utility in that they can be used as "minus targets" in screens designed to identify compounds that specifically interact with other ion channels. For example, Wang et al., 1998, Science 282:1890-1893 have shown that KCNQ2 and KCNQ3 form a heteromeric potassium ion channel known as the "M-channel." The M-channel is an important target for drug discovery since mutations in KCNQ2 and KCNQ3 are responsible for causing epilepsy (Biervert et al., 1998, Science 279:403-406; Singh et al., 1998, Nature Genet. 18:25-29; Schroeder et al., Nature 1998, 396:687-690). A screening program designed to identify activators or inhibitors of the M-channel would benefit greatly by the use of KCNQ5 as a minus target.

The present invention also includes antibodies to the KCNQ5 protein. Such antibodies may be polyclonal antibodies or monoclonal antibodies. The antibodies of the present invention are raised against the entire KCNQ5 protein or against suitable antigenic fragments of the protein that are coupled to suitable carriers, *e.g.*, serum albumin or keyhole limpet hemocyanin, by methods well known in the art. Methods of identifying suitable antigenic fragments of a protein are known in the art. See, *e.g.*, Hopp & Woods, 1981, Proc. Natl. Acad. Sci. USA 78:3824-3828; and Jameson & Wolf, 1988, CABIOS (Computer Applications in the Biosciences) 4:181-186.

For the production of polyclonal antibodies, KCNQ5 protein or an antigenic fragment, coupled to a suitable carrier, is injected on a periodic basis into an appropriate non-human host animal such as, *e.g.*, rabbits, sheep, goats, rats, mice. The animals are bled periodically and sera obtained are tested for the presence of antibodies to the injected antigen. The injections can be intramuscular, intraperitoneal, subcutaneous, and the like, and can be accompanied with adjuvant.

For the production of monoclonal antibodies, KCNQ5 protein or an antigenic fragment, coupled to a suitable carrier, is injected into an appropriate non-human host animal as above for the production of polyclonal antibodies. In the case

of monoclonal antibodies, the animal is generally a mouse. The animal's spleen cells are then immortalized, often by fusion with a myeloma cell, as described in Kohler & Milstein, 1975, Nature 256:495-497. For a fuller description of the production of monoclonal antibodies, see Antibodies: A Laboratory Manual, Harlow & Lane, eds.,

5 Cold Spring Harbor Laboratory Press, 1988.

Gene therapy may be used to introduce KCNQ5 polypeptides into the cells of target organs, *e.g.*, the pigmented epithelium of the retina or other parts of the retina. Nucleotides encoding KCNQ5 polypeptides can be ligated into viral vectors which mediate transfer of the nucleotides by infection of recipient cells. Suitable

10 viral vectors include retrovirus, adenovirus, adeno-associated virus, herpes virus, vaccinia virus, lentivirus, and polio virus based vectors. Alternatively, nucleotides encoding KCNQ5 polypeptides can be transferred into cells for gene therapy by non-viral techniques including receptor-mediated targeted transfer using ligand-nucleotide

15 conjugates, lipofection, membrane fusion, or direct microinjection. These procedures and variations thereof are suitable for *ex vivo* as well as *in vivo* gene therapy. Gene therapy with KCNQ5 polypeptides will be particularly useful for the treatment of diseases where it is beneficial to elevate KCNQ5 activity.

The present invention includes processes for cloning orthologues of human KCNQ5 from non-human species. In general, such processes include

20 preparing a PCR primer or a hybridization probe based upon SEQ.ID.NO.:1 or SEQ.ID.NO.:2 that can be used to amplify a fragment containing the non-human KCNQ5 (in the case of PCR) from a suitable DNA preparation or to select a cDNA or genomic clone containing the non-human KCNQ5 from a suitable library. A preferred embodiment of this process is a process for cloning the KCNQ5 gene from

25 mouse.

By providing DNA encoding mouse KCNQ5, the present invention allows for the generation of an animal model of Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration. Such animal

30 models can be generated by making transgenic "knockout" or "knockin" mice containing altered KCNQ5 genes. Knockout mice can be generated in which portions of the mouse KCNQ5 gene have been deleted. Knockin mice can be generated in which mutations that have been shown to lead to Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration when present in the human KCNQ5 gene are introduced into the mouse gene. Such knockout and

knockin mice will be valuable tools in the study of Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration and will provide important model systems in which to test potential pharmaceuticals or treatments for Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration.

Accordingly, the present invention includes a method of producing a mouse model of Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration comprising:

- (a) designing PCR primers or an oligonucleotide probe based upon SEQ.ID.NO.:1 or SEQ.ID.NO.:2 for use in cloning the mouse KCNQ5 gene;
- (b) using the PCR primers or the oligonucleotide probe to clone at least a portion of the mouse KCNQ5 gene, the portion being large enough to use in making a transgenic mouse;
- (c) producing a transgenic mouse having at least one copy of the mouse KCNQ5 gene altered from its native state.

Methods of producing knockout and knockin mice are well known in the art. One method involves the use of gene-targeted ES cells in the generation of gene-targeted transgenic knockout mice and is described in, *e.g.*, Thomas et al., 1987, Cell 51:503-512, and is reviewed elsewhere (Frohman et al., 1989, Cell 56:145-147; Capecchi, 1989, Trends in Genet. 5:70-76; Baribault et al., 1989, Mol. Biol. Med. 6:481-492).

Techniques are available to inactivate or alter any genetic region to virtually any mutation desired by using targeted homologous recombination to insert specific changes into chromosomal genes. Generally, use is made of a "targeting vector," *i.e.*, a plasmid containing part of the genetic region it is desired to mutate. By virtue of the homology between this part of the genetic region on the plasmid and the corresponding genetic region on the chromosome, homologous recombination can be used to insert the plasmid into the genetic region, thus disrupting the genetic region. Usually, the targeting vector contains a selectable marker gene as well.

In comparison with homologous extrachromosomal recombination, which occurs at frequencies approaching 100%, homologous plasmid-chromosome recombination was originally reported to only be detected at frequencies between 10^{-6} and 10^{-3} (Lin et al., 1985, Proc. Natl. Acad. Sci. USA 82:1391-1395; Smithies et al., 1985, Nature 317: 230-234; Thomas et al., 1986, Cell 44:419-428).

Nonhomologous plasmid-chromosome interactions are more frequent, occurring at levels 10⁵-fold (Lin et al., 1985, Proc. Natl. Acad. Sci. USA 82:1391-1395) to 10²-fold (Thomas et al., 1986, Cell 44:419-428) greater than comparable homologous insertion.

- 5 To overcome this low proportion of targeted recombination in murine ES cells, various strategies have been developed to detect or select rare homologous recombinants. One approach for detecting homologous alteration events uses the polymerase chain reaction (PCR) to screen pools of transformant cells for homologous insertion, followed by screening individual clones (Kim et al., 1988, 10 Nucleic Acids Res. 16:8887-8903; Kim et al., 1991, Gene 103:227-233). Alternatively, a positive genetic selection approach has been developed in which a marker gene is constructed which will only be active if homologous insertion occurs, allowing these recombinants to be selected directly (Sedivy et al., 1989, Proc. Natl. Acad. Sci. USA 86:227-231). One of the most powerful approaches developed for 15 selecting homologous recombinants is the positive-negative selection (PNS) method developed for genes for which no direct selection of the alteration exists (Mansour et al., 1988, Nature 336:348-352; Capecchi, 1989, Science 244:1288-1292; Capecchi, 1989, Trends in Genet. 5:70-76). The PNS method is more efficient for targeting genes which are not expressed at high levels because the marker gene has its own 20 promoter. Nonhomologous recombinants are selected against by using the Herpes Simplex virus thymidine kinase (HSV-TK) gene and selecting against its nonhomologous insertion with herpes drugs such as gancyclovir (GANC) or FIAU (1-(2-deoxy 2-fluoro-B-D-arabinofluranosyl)-5-iodouracil). By this counter-selection, the percentage of homologous recombinants in the surviving transformants can be 25 increased.

Other methods of producing transgenic mice involve microinjecting the male pronuclei of fertilized eggs. Such methods are well known in the art.

- The following non-limiting examples are presented to better illustrate 30 the invention.

EXAMPLE 1

Identification of the human KCNQ5 gene and cDNA cloningConstruction of Libraries for Shotgun Sequencing from PAC Clones

- Bacterial strains containing the KCNQ5 PACs (P1 Artificial Chromosomes) were received from Research Genetics (Huntsville, AL). Cells were streaked on Luria-Bertani (LB) agar plates supplemented with the appropriate antibiotic. A single colony was used to prepare a 5-ml starter culture and then 1-L overnight culture in LB medium. The cells were pelleted by centrifugation and PAC DNA was purified by equilibrium centrifugation in cesium chloride-ethidium bromide gradient (Sambrook, Fritsch, and Maniatis, 1989, Molecular Cloning: A Laboratory Manual, second edition, Cold Spring Harbor Laboratory Press). Purified PAC DNA was brought to 50 mM Tris pH 8.0, 15 mM MgCl₂, and 25% glycerol in a volume of 2 ml and placed in a AERO-MIST nebulizer (CIS-US, Bedford, MA). The nebulizer was attached to a nitrogen gas source and the DNA was randomly sheared at 10 psi for 30 sec. The sheared DNA was ethanol precipitated and resuspended in TE (10 mM Tris, 1 mM EDTA). The ends were made blunt by treatment with Mung Bean Nuclease (Promega, Madison, WI) at 30°C for 30 min, followed by phenol/chloroform extraction, and treatment with T4 DNA polymerase (GIBCO/BRL, Gaithersburg, MD) in multicore buffer (Promega, Madison, WI) in the presence of 40 µM dNTPs at 16°C. To facilitate subcloning of the DNA fragments, BstX I adapters (Invitrogen, Carlsbad, CA) were ligated to the fragments at 14°C overnight with T4 DNA ligase (Promega, Madison, WI). Adapters and DNA fragments less than 500 bp were removed by column chromatography using a cDNA sizing column (GIBCO/BRL, Gaithersburg, MD) according to the instructions provided by the manufacturer. Fractions containing DNA greater than 1 kb were pooled and concentrated by ethanol precipitation. The DNA fragments containing BstX I adapters were ligated into the BstX I sites of pSHOT II which was constructed by subcloning the BstX I sites from pcDNA II (Invitrogen, Carlsbad, CA) into the BssH II sites of pBlueScript (Stratagene, La Jolla, CA). pSHOT II was prepared by digestion with BstX I restriction endonuclease and purified by agarose gel electrophoresis. The gel purified vector DNA was extracted from the agarose by following the Prep-A-Gene (BioRad, Richmond, CA) protocol. To reduce ligation of

the vector to itself, the digested vector was treated with calf intestinal phosphatase (GIBCO/BRL, Gaithersburg, MD. Ligation reactions of the DNA fragments with the cloning vector were transformed into ultra-competent XL-2 Blue cells (Stratagene, La Jolla, CA), and plated on LB agar plates supplemented with 100 µg/ml ampicillin.

- 5 Individual colonies were picked into a 96 well plate containing 100 µl/well of LB broth supplemented with ampicillin and grown overnight at 37°C. Approximately 25 µl of 80% sterile glycerol was added to each well and the cultures stored at -80°C.

Preparation of plasmid DNA

- 10 Glycerol stocks were used to inoculate 5 ml of LB broth supplemented with 100 µg/ml ampicillin either manually or by using a Tecan Genesis RSP 150 robot (Tecan AG, Hombrechtikon, Switzerland) programmed to inoculate 96 tubes containing 5 ml broth from the 96 wells. The cultures were grown overnight at 37°C with shaking to provide aeration. Bacterial cells were pelleted by centrifugation, the
15 supernatant decanted, and the cell pellet stored at -20°C. Plasmid DNA was prepared with a QIAGEN Bio Robot 9600 (QIAGEN, Chatsworth, CA) according to the Qiawell Ultra protocol. To test the frequency and size of inserts, plasmid DNA was digested with the restriction endonuclease Pvu II. The size of the restriction endonuclease products was examined by agarose gel electrophoresis with the average
20 insert size being 1 to 2 kb.

DNA Sequence Analysis of Shotgun clones

- DNA sequence analysis was performed using the ABI PRISM™ dye terminator cycle sequencing ready reaction kit with AmpliTaq DNA polymerase, FS
25 (Perkin Elmer, Norwalk, CT). DNA sequence analysis was performed with M13 forward and reverse primers. Following amplification in a Perkin-Elmer 9600, the extension products were purified and analyzed on an ABI PRISM 377 automated sequencer (Perkin Elmer, Norwalk, CT). Approximately 4 sequencing reactions were performed per kb of DNA to be examined (384 sequencing reactions per each of nine
30 PACs).

Assembly of DNA sequences

Phred/Phrap was used for DNA sequences assembly. This program was developed by Dr. Phil Green and licensed from the University of Washington

(Seattle, WA). Phred/Phrap consists of the following programs: Phred for base-calling, Phrap for sequence assembly, Crossmatch for sequence comparisons, Consed and Phrapview for visualization of data, Repeatmasker for screening repetitive sequences. Vector and *E. coli* DNA sequences were identified by Crossmatch and removed from the DNA sequence assembly process. DNA sequence assembly was on a SUN Enterprise 4000 server running a Solaris 2.51 operating system (Sun Microsystems Inc., Mountain View, CA) using default Phrap parameters. The sequence assemblies were further analyzed using Consed and Phrapview.

10 Genomic sequence of the KCNQ5 gene and its exon/intron organization

Genomic DNA sequence from PAC 141B1 was compared with GenBank database entries using the BLASTN and BLASTX algorithms of the AceDB package. This comparison originally revealed a total of 5 exons (exons 3(D), 4 (A), 5(B), 6(E), and 7(C) delineated in Figure1), based on their homology to the known potassium channel genes KCNQ1, KCNQ2, KCNQ3, and KCNQ4. Full-length cDNA was rescued from the pools of the human fetal brain cDNA library using the RCCA technique described in Example 2. Comparison of the cDNA sequence and genomic sequence of PAC141B1 revealed a total of 8 exons (exons 3-10 delineated in Figure1). Genomic regions corresponding to exons 1,2, and 11-14 were not present in PAC141B1.

In order to identify the genomic region corresponding to exon 2 and its right flanking intron, oligonucleotide KCN-2L2 (TTTTCTCCTTGCTTTGGTTGCTTG; SEQ.ID.NO.:11) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-2L1 (CCTCAAGTTGCCTCTTGATCCTG; SEQ.ID.NO.:13) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 2 and its left flanking intron, oligonucleotide KCN-2R1 (CAGGATCAAGAGGCAACTTGAGG; SEQ.ID.NO.:15) from the KCNQ5 cDNA in combination with the adaptor primer AP1

(CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-2R2 (CCAATTTTGTGTGCTCAGGGATGGTAGA; SEQ.ID.NO.:16) in
 5 combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 11 and its right flanking intron, oligonucleotide KCN-11L1 (GACACAGCCCTTGGCACT; SEQ.ID.NO.:17) from the KCNQ5 cDNA in combination with the adaptor primer
 10 API (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-11L2 (GATGATGTATATGATGAAAAAGGATG; SEQ.ID.NO.:18) in
 combination with the nested adaptor primer AP2
 15 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 11 and its left flanking intron, oligonucleotide KCN-11R1 (CTGATAGCTCGAATGACAGTTTT; SEQ.ID.NO.:19) from the KCNQ5 cDNA in
 combination with the adaptor primer AP1
 20 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN11-R2 (AAGTGGTGGGGTGAGGTCTTCCACTG; SEQ.ID.NO.:20) in
 combination with the nested adaptor primer AP2
 25 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 12 and its right flanking intron, oligonucleotide KCN-12L1 (AGA ATT ATG AAA TTT CAT GTT GCA; SEQ.ID.NO.:21) from the KCNQ5 cDNA in combination with the
 adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12)
 30 was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-12L2 (AAA CGG AAG TTT AAG GAA ACA TT; SEQ.ID.NO.:22) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 12 and its left flanking intron, oligonucleotide KCN-12R1 (ACG TGT TTG TTG GCT TTT AAT TC; SEQ.ID.NO.:23) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-12R2 (TAC ACA ACA TGT CCA GAT GAC; SEQ.ID.NO.:24) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 13 and its right flanking intron, oligonucleotide KCN-13L1 (TGATCAAATTCTTGAAAAGGG; SEQ.ID.NO.:25) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-13L2 (TCACATCAGATAAGAAGAGCCGA; SEQ.ID.NO.:26) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 13 and its left flanking intron, oligonucleotide KCN-13R1 (GTTTTTCAACCTTGACCACCC; SEQ.ID.NO.:27) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-13R2 (AGCATACTGAGATCGTCTGTGGT; SEQ.ID.NO.:28) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 14 and its left flanking intron, oligonucleotide KCN-2543R (AATTCCAAAAGTGTCTGTCTCTGTC; SEQ.ID.NO.:29) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-

amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-2512R (GGACCCACCTCTTCATCAGTTA; SEQ.ID.NO.:30) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC;

5 SEQ.ID.NO.:14).

Products obtained from these PCR amplifications were analyzed using ABI 377 sequencers according to standard protocols. Comparison of the full-length KCNQ5 cDNA sequence with the sequences of PAC141B1 and sequences obtained in PCR reactions with DNA from the GenomeWalker kit revealed all 14 exons of the
10 KCNQ5 gene. Exact sequence of exon/intron boundaries within the KCNQ5 gene were determined for exons 2-14. The splice signals in all introns conform to published consensus sequences.

EXAMPLE 2

15 Cloning of KCNQ5 cDNA

The DNA sequence of the cDNA fragment that matches exons 3(D), 4 (A), 5(B), 6(E), and 7(C) of the KCNQ5 was deduced from the genomic sequence of PAC 141B1. Subsequent sequencing of PCR fragments obtained in RCCA reactions confirmed the presence of this fragment in the cDNA library from human
20 fetal brain. This original cDNA fragment corresponds to the cDNA region with coordinates 368-1,004 in Figure 2.

A PCR based technique termed Reduced Complexity cDNA Analysis (RCCA) was used to extend this original cDNA fragment. RCCA is similar to procedures reported by Munroe et al., 1995, Proc. Natl. Acad. Sci. USA 92: 2209-
25 2213 and Wilfinger et al., 1997, BioTechniques 22:481-486 and relies upon a PCR template that is a pool of approximately 20,000 cDNA clones; this reduces the complexity of the template and increases the probability of obtaining longer PCR extensions.

96 wells of a human fetal brain plasmid library were scanned, 20,000
30 clones per well, by amplifying a 483 bp PCR product using primers KCN-DL (GGAAGACTGAGGTTTGCTCG; SEQ.ID.NO.31) and KCN-ER (GGCAGGAAGTGCAAAGAAAG; SEQ.ID.NO.32). Eight wells were found to

contain the correct 483 bp fragment by PCR analysis. 5' and 3' RACE was subsequently performed on the positive wells containing the plasmid cDNA library using a vector specific primer and a gene specific primer. The vector specific primers, PBS 543R (GGGGATGTGCTGCAAGGCGA; SEQ.ID.NO.33) and PBS 873F (CCCAGGCTTTACACTTTATGCTTCC; SEQ.ID.NO.34) were both used in combination with gene specific primers KCN-DL and KCN-ER because the orientation of the insert was not known. After the initial PCR amplification, a nested PCR reaction was performed using nested vector primers PBS 578R (CCAGGGTTTTCCCAAGTCACGAC; SEQ.ID.NO.35) and PBS 838F (TTGTGTGGAATTGTGAGCGGATAAC; SEQ.ID.NO.36) and gene specific primers KCN-EL (CTTTCTTTGCACTTCCTGCC; SEQ.ID.NO.37) and KCN-DR1 (AACACAGAAGGGCTTTCGAG; SEQ.ID.NO.38). The PCR products were separated from the unincorporated dNTP's and primers using Qiagen, QIAquick PCR purification spin columns using standard protocols and resuspended in 30 µl of water. The products were analyzed on ABI 377 sequencers according to standard protocols.

PCR fragments were assembled into a contig termed "KCN consensus 2_16_99" that corresponds to the cDNA region with coordinates 278-1,456 in Figure 2. A second round of the RCCA analysis was performed to obtain the clones extending to the 3' end of the cDNA contig termed "KCN consensus 2_16_99". 96 wells of a human fetal brain plasmid library were scanned, 20,000 clones per well, by amplifying a 117 bp PCR product using primers KCN-11L1 (GACACAGCCCTTGGCACT; SEQ.ID.NO.17) and KCN-11R1 (CTGATAGCTCGAATGACAGTTTT; SEQ.ID.NO.19) that were derived from the 3' sequence of the cDNA contig termed "KCN consensus 2_16_99". A number of wells were found to contain the correct 117 bp fragment by PCR analysis. 3' RACE was subsequently performed on the positive wells containing the plasmid cDNA library using a vector specific primer and a gene specific primer. The vector specific primers, PBS 543R (GGGGATGTGCTGCAAGGCGA; SEQ.ID.NO.33) and PBS 873F (CCCAGGCTTTACACTTTATGCTTCC; SEQ.ID.NO.34) were both used in combination with gene specific primer KCN-11L1 (GACACAGCCCTTGGCACT; SEQ.ID.NO.17) because the orientation of the insert was not known. After the initial PCR amplification, a nested PCR reaction was performed using nested vector primers PBS 578R (CCAGGGTTTTCCCAAGTCACGAC; SEQ.ID.NO.35) and PBS 838F (TTGTGTGGAATTGTGAGCGGATAAC; SEQ.ID.NO.36) and gene specific primer

KCN11-R2 (AAGTGGTGGGGTGAGGTCTTCCACTG; SEQ.ID.NO.20). The PCR products were separated from the unincorporated dNTPs and primers using Qiagen, QIAquick PCR purification spin columns using standard protocols and resuspended in 30 µl of water. The products were analyzed on ABI 377 sequencers according to standard protocols.

5 PCR fragments were assembled into a contig termed "KCN consensus 2_26_99" that corresponds to the cDNA region with coordinates 278-2,527 in Figure 2. A third round of RCCA analysis was performed to obtain the clones extending to the 5' end of the cDNA contig termed "KCN consensus 2_26_99". 96 wells of a human fetal brain plasmid library were scanned, 20,000 clones per well, by amplifying a 214 bp PCR product using primers KCN-2L2 (TTTTCTCCTTGTCTTTGGTTGCTTG; SEQ.ID.NO.11) and KCN-DR1 (AACACAGAAGGGCTTTCGAG; SEQ.ID.NO.38) that were derived from the 5' sequence of the cDNA contig termed "KCN consensus 2_26_99". A number of wells were found to contain the correct 214 bp fragment by PCR analysis. 5' RACE was subsequently performed on the positive wells containing the plasmid cDNA library using a vector specific primer and a gene specific primer. The vector specific primers, PBS 543R (GGGGATGTGCTGCAAGGCGA; SEQ.ID.NO.33) and PBS 873F (CCCAGGCTTTACACTTTATGCTTCC; SEQ.ID.NO.34) were both used in combination with gene specific primer KCN-DR1 (AACACAGAAGGGCTTTCGAG; SEQ.ID.NO.38) because the orientation of the insert was not known. After the initial PCR amplification, a nested PCR reaction was performed using nested vector primers PBS 578R (CCAGGGTTTCCCAGTCACGAC; SEQ.ID.NO.35) and PBS 838F (TTGTGTGGAATTGTGAGCGGATAAC; SEQ.ID.NO.36) and gene specific primer KCN-DR2 (CAGTCTTCCTTGCCATCCTC; SEQ.ID.NO.39). The PCR products were separated from the unincorporated dNTPs and primers using Qiagen, QIAquick PCR purification spin columns using standard protocols and resuspended in 30 µl of water. The products were analyzed on ABI 377 sequencers according to standard protocols.

30 PCR fragments were assembled into a contig termed "KCN consensus 3_3_99" that corresponds to the cDNA region with coordinates 1-2,527 in Figure 2. A fourth round of RCCA analysis was performed to obtain the clones extending to the 3' end of the cDNA contig termed "KCN consensus 3_3_99". 96 wells of a human

fetal brain plasmid library were scanned, 20,000 clones per well, by amplifying a 145 bp PCR product using primers KCN-2106L (GCAGCCCCAACAACCTTTACA; SEQ.ID.NO.40) and KCN-2250R (CATTTTCCTTGGAGGCAACA; SEQ.ID.NO.41) that were derived from the 3' sequence of the cDNA contig termed "KCN consensus 3_3_99". A number of wells were found to contain the correct 214 bp fragment by PCR analysis. 5' RACE was subsequently performed on the positive wells containing the plasmid cDNA library using a vector specific primer and a gene specific primer. The vector specific primers, PBS 543R (GGGGATGTGCTGCAAGGCGA; SEQ.ID.NO.33) and PBS 873F (CCCAGGCTTTACACTTTATGCTTCC; SEQ.ID.NO.34) were both used in combination with gene specific primer KCN-2106L (GCAGCCCCAACAACCTTTACA; SEQ.ID.NO.40) because the orientation of the insert was not known. After the initial PCR amplification, a nested PCR reaction was performed using nested vector primers PBS 578R (CCAGGGTTTTCCCAGTCACGAC; SEQ.ID.NO.35) and PBS 838F (TTGTGTGGAATTGTGAGCGGATAAC; SEQ.ID.NO.36) and gene specific primer KCN-2165L (GCCAGAACTCTGCACCCTA; SEQ.ID.NO.42). The PCR products were separated from the unincorporated dNTP's and primers using Qiagen, QIAquick PCR purification spin columns using standard protocols and resuspended in 30 µl of water. The products were analyzed on ABI 377 sequencers according to standard protocols; PCR fragments were assembled into a contig termed "KCN consensus 3_15_99" that corresponds to the cDNA sequence depicted in Figure 2.

EXAMPLE 3

25 Analysis of expression of KCNO5

RT-PCR: RT-PCR experiments were performed on "quick-clone" human cDNA samples available from Clontech, Palo Alto, CA. cDNA samples from heart, brain, placenta, lung, liver, skeletal muscle, kidney, pancreas, and retina were amplified with primers KCN-DL (GGAAGACTGAGGTTTGCTCG; SEQ.ID.NO.31) and KCN-ER (GGCAGGAAGTGCAAAGAAAG; SEQ.ID.NO.32) in the following PCR conditions:

1. 94°C 10 min
2. 94°C 30 sec
3. 72°C 2 min (decrease this temperature by 1.1°C per cycle)
4. 72°C 2 min
- 5 5. Go to step 2 21 more times
6. 94°C 30 sec
7. 55°C 2 min
8. 72°C 2 min
9. Go to step 6 19 more times
- 10 10. 72°C 7 min
11. 4°C

The KCNQ5 gene was found to be predominantly expressed in human retina and brain (Figure 3B).

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Northern blot analysis: Northern blots containing poly(A+)-RNA from human heart, brain, placenta, lung, liver, skeletal muscle, kidney, pancreas were purchased from Clontech, Palo Alto, CA. Primers KCN-DL (GGAAGACTGAGGTTTGCTCG; SEQ.ID.NO.31) and KCN-ER (GGCAGGAAGTGCAAAGAAAG; SEQ.ID.NO.32) were used to amplify a PCR product of 483 bp from a quick-clone human retina cDNA available from Clontech, Palo Alto, CA. This fragment was purified on an agarose gel, the DNA extracted and used as a probe for Northern blot hybridization.

The probe was labeled by random priming with the Amersham Rediprime kit (Arlington Heights, IL) in the presence of 50-100 μ Ci of 3000 Ci/mmol $[\alpha\text{-}^{32}\text{P}]\text{dCTP}$ (Dupont/NEN, Boston, MA). Unincorporated nucleotides were removed with a ProbeQuant G-50 spin column (Pharmacia/Biotech, Piscataway, NJ). The radiolabeled probe at a concentration of greater than 1×10^6 cpm/ml in rapid hybridization buffer (Clontech, Palo Alto, CA) was incubated overnight at 65°C. The blots were washed by two 15 min incubations in 2X SSC, 0.1% SDS (prepared from 20X SSC and 20 % SDS stock solutions, Fisher, Pittsburgh, PA) at room temperature, followed by two 15 min incubations in 1X SSC, 0.1% SDS at room temperature, and two 30 min incubations in 0.1X SSC, 0.1% SDS

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at 60°C. Autoradiography of the blots was done to visualize the bands that specifically hybridized to the radiolabeled probe.

The probe hybridized to an mRNA transcript that is predominately expressed in brain and retina (Figure 3A).

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The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

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Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

WHAT IS CLAIMED IS:

1. An isolated DNA comprising nucleotides encoding a KCNQ5 protein.
- 5 2. The DNA of claim 1 comprising nucleotides encoding a polypeptide having the amino acid sequence SEQ.ID.NO.:3.
- 10 3. The DNA of claim 1 comprising a nucleotide sequence selected from the group consisting of: SEQ.ID.NO.:1, SEQ.ID.NO.:2, and positions 138-2,675 of SEQ.ID.NO.:2.
- 15 4. An isolated DNA that hybridizes under stringent conditions to a nucleotide sequence selected from the group consisting of: SEQ.ID.NO.:1 and SEQ.ID.NO.:2.
5. An expression vector comprising the DNA of claim 1.
6. A recombinant host cell comprising the DNA of claim 1.
- 20 7. An isolated KCNQ5 protein.
8. The KCNQ5 protein of claim 7 having the amino acid sequence SEQ.ID.NO.: 3.
- 25 9. The KCNQ5 protein of claim 8 containing a single amino acid substitution.
10. The KCNQ5 protein of claim 8 containing two or more amino acid substitutions where the amino acid substitutions do not occur in a position where the amino acid substituted in KCNQ5 is also present in the corresponding position of any one of KCNQ2, KCNQ3, or KCNQ4.
- 30

11. An antibody that binds specifically to a KCNQ5 protein where the KCNQ5 protein has the amino acid sequence SEQ.ID.NO.:3.

12. A method of diagnosing whether a patient has Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration that comprises determining the DNA sequence of a region of the KCNQ5 gene from the patient and comparing that sequence to the sequence from the corresponding region of the KCNQ5 gene from a non-affected person, *i.e.*, a person who does not have Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration, where a difference in sequence between the DNA sequence of the KCNQ5 gene from the patient and the DNA sequence of the KCNQ5 gene from the non-affected person indicates that the patient has Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration.

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13. A method of diagnosing whether a patient carries a mutation in the KCNQ5 gene that comprises:

- (a) providing a DNA sample from the patient;
- (b) providing a set of PCR primers based upon SEQ.ID.NO.:1 or SEQ.ID.NO.:2;
- (c) performing PCR on the DNA sample to produce a PCR fragment from the patient;
- (d) determining the nucleotide sequence of the PCR fragment from the patient;
- (e) comparing the nucleotide sequence of the PCR fragment from the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2; where a difference between the nucleotide sequence of the PCR fragment from the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2 indicates that the patient carries a mutation in the KCNQ5 gene.

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14. The method of claim 13 where the DNA sample is genomic DNA.

15. The method of claim 13 where the DNA sample is cDNA.

16. A DNA or RNA oligonucleotide probe comprising at least 18 contiguous nucleotides of at least one of a sequence selected from the group consisting of: SEQ.ID.NO.:1 and SEQ.ID.NO.:2.

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17. A method for determining whether a substance is an activator or an inhibitor of a KCNQ5 protein or a mutant KCNQ5 protein comprising:

- (a) recombinantly expressing KCNQ5 protein or mutant KCNQ5 protein in a host cell;
- 10 (b) measuring the biological activity of KCNQ5 protein or mutant KCNQ5 protein in the presence and in the absence of a substance suspected of being an activator or an inhibitor of KCNQ5 protein or mutant KCNQ5 protein; where a change in the biological activity of the KCNQ5 protein or the mutant KCNQ5 protein in the presence as compared to the absence of the substance
15 indicates that the substance is an activator or an inhibitor of KCNQ5 protein or mutant KCNQ5 protein.

18. A method of identifying inhibitors of KCNQ5 comprising:

- (a) expressing KCNQ5 protein in *Xenopus* oocytes;
- 20 (b) changing the transmembrane potential of the oocytes in the presence and the absence of a substance suspected of being an inhibitor of KCNQ5;
- (c) measuring membrane potassium currents following step (b); where if the potassium membrane currents measured in step (c) are
25 greater in the absence rather than in the presence of the substance, then the substance is an inhibitor of KCNQ5.

19. A method of identifying activators of KCNQ5 comprising:

- (a) providing test cells comprising:
 - (1) an expression vector that directs the expression of
30 KCNQ5 in the cells;
 - (2) a first fluorescent dye, where the first dye is bound to one side of the plasma membrane; and

(3) a second fluorescent dye, where the second fluorescent dye is free to shuttle from one face of the plasma membrane to the other face in response to changes in membrane potential;

(b) exposing the test cells to a substance that is suspected of being an activator of KCNQ5;

(c) measuring the amount of fluorescence resonance energy transfer (FRET) in the test cells that have been exposed to the substance;

(d) comparing the amount of FRET exhibited by the test cells that have been exposed to the substance with the amount of FRET exhibited by control cells;

wherein if the amount of FRET exhibited by the test cells is greater than the amount of FRET exhibited by the control cells, the substance is an activator of KCNQ5;

where the control cells are either (1) cells that are essentially the same as the test cells except that they do not comprise at least one of the items listed at (a) (1)-(3) but have been exposed to the substance; or (2) test cells that have not been exposed to the substance.

20. A method of identifying inhibitors of KCNQ5 comprising:

(a) providing test cells comprising:

(1) an expression vector that directs the expression of KCNQ5 in the cells;

(2) a first fluorescent dye, where the first dye is bound to one side of the plasma membrane; and

(3) a second fluorescent dye, where the second fluorescent dye is free to shuttle from one face of the plasma membrane to the other face in response to changes in membrane potential;

(b) exposing the test cells to a substance that is suspected of being an inhibitor of KCNQ5;

(c) measuring the amount of fluorescence resonance energy transfer (FRET) in the test cells that have been exposed to the substance;

(d) comparing the amount of FRET exhibited by the test cells that have been exposed to the substance with the amount of FRET exhibited by control cells;

wherein if the amount of FRET exhibited by the test cells is less than the amount of FRET exhibited by the control cells, the substance is an inhibitor of KCNQ5;

5 where the control cells are either (1) cells that are essentially the same as the test cells except that they do not comprise at least one of the items listed at (a) (1)-(3) but have been exposed to the substance; or (2) test cells that have not been exposed to the substance.

21. A method of treating Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, age-related macular degeneration, other forms of
10 macular degeneration, deafness, epilepsy, different forms of neuropsychiatric, heart, gastrointestinal, and muscle disorders by administering to a patient a therapeutically effective amount of a substance that is an activator or an inhibitor of a voltage-gated potassium channel containing the KCNQ5 protein.

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FIGURE 1A

KCN6q gene: DNA sequence

1. Underlined nucleotides in capitals represent exons.
2. Initiating ATG codon in exon 1 and terminating TAA codon in exon 14 are shown in bold italics
3. D6D280 genetic marker and phosphoglycerate mutase pseudogene are bold underlined
4. The exact lengths of the gaps between exons 1 and 2, 2 and 3, 10 and 11, 11 and 12, 12 and 13, 13 and 14 are unknown; these gaps are presented as runs of ten **bold n** as a convenience only

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1  CTGGAGTGAG GCGCGGGAAG ATGCTTGGTC CTTGCCTCGC GGACTTGGCA
51  GCCGCGTCCT GCGGGTCTGT CCACTGAACT GCTGAGGACT GCGGCGGTGG
101 CCTGAGGGAG AGCCGCGGGG GCAAGCAGGG GCGCGGATG AGCCTGCTGG
151 GGAAGCCGCT CTCTACACG AGTAGCCAGA GCTGCGGGCG CAACGTCAAG
201 TACCGGCGGG TGCAGPACTA CCTGTACAAC GTGCTGGAGA GACCCGCGCG
251 CTGGGCGTTC ATCTACCAGC CTTCGThnn nnnnnnttc cttttctatt
301 cttattatta atatatgac ttattattaa taatataaag gaatagcaaa
351 tgagaatcca tgagcaatat cagaccatga aaatgagcca gtggctgagt
401 aacaaccaat taggacactt gatagtttag caaagttgcc aaacaggaga
451 cagactcggc tcctttgaac gaagagtgc tgcagtgtgg attccccaga
501 taggagagca agaacatact ttctgggcct ctctcaggat cgttgtttgg
551 gaaggaagtt gtatgggaaa ttcacaaact cttagatgct aacatttaaa
601 tgcagcatgc cacacacaca aaccacaaa cacaacctt tttcatcaa
651 taaaattgca gaggagcccc atttgacag tatatcacat tgtattttaa
701 tatccaaaat ggctagtccc ttccagagtt tttatgagtt aatgtgtgct
751 aatttaattg gcctgtgtct ttattcattt gaagcaagaa attaagtctg
801 tgataataag gtaaggttct tatcagattt ctctttttgt tgttttacag
851 TTTTCTCCTT GTCCTTGGTT GCTTGATTTT GTCAGTGTTC TCTACCATCC
901 CTGAGCACAC AAAATTGGCC TCAAGTTGCC TCTTGATCCT Ggtaagtga
951 acatgaacaa gaacgtacat gaatgttgta taagaactgc ctataacatt
1001 tatactatgc atcttatcct acaaaaaaat cctatctaaa aaagagttac
1051 tgagaaatat aaaaatgtca aagattactg aaacatttgc ccaccaattt
1101 aacatgtagt caatccttag aaatatatag aaatgttcag gattgctatt
1151 acacagcaat atcttgtgtt gtagatataat cataaataga aggcaatatt
1201 agaaagcagt tttaaagtatg tttatctatg ctaataaaca aattatataa
1251 gaagaatcag tatctatgag gcctctcatt atattgtgaa agactataga
1301 gttagagagca ttttccaata actgtaattt ggcagtagct aaatataatt
1351 ggccaagaac tatgaacata tggcacctca taagaaaata gaaggctcct
1401 tcatgctcct ttcaaccaac agactgcatt atgagttttg ctgctaattg
1451 agttacctgg tgataaattc tgcagtttgc tctgtttcca ttatgctgtc
1501 aatcctcaac cacacagaat tgcctcaatt actttnnnnn nnnnnnacgag
1551 gtcaggaggt cgagaccatc ctgcctaaca cgggtgaaacc ccgcctctac
1601 taaaaataca aaaaattagc tgggcgtagc tactcaggag gctgaggcag
1651 gagaatggcg tgaacctggg aggcggagct tgcagtgagc cgagattgag
1701 tcaactgcact ccagcgacag agccagactc cgtctcaaaa aaaaaaaaaa
1751 aaaaaaaaaa gagtatactt gatttatggc atgagtggtc ttgaatgatt
1801 ttgatggatg actggaaaca attagagata taaataaata gcacagaatc
1851 atgacagatt tcatgaagaa tacactgtga agattcacat ggttaataac
1901 attgaaatta ttaaaataaa agagactgca tatattagat tttctttgt
1951 gatctagttg ttcaaagcag cagaaaactt taaattttcc ttaattttga
2001 aagtgtgatt aatggaatat tgttacaatg ccattgattt atatactttg
2051 aggatagtta acttctttat gtttattaga aattgcactg agagctaata
2101 tgcagtttct attgtgtgtg atatgtttctg ttaacagggc ctctgtcag
2151 tttttattct gagattttctg cctttctctgt tcttttgcat gacctaact
2201 gactgagttt caatatcaag ttctgaaagc aagtgagcat actagtgtgc
2251 atgcaatgtg cacagaaaga tgtgttttcc tacctctcaa agctcaccaa
2301 aggatattac tcatattgcc acaaagtaca ttacaccaa taacacatac
2351 tttggtaatg ggaaaaataa ataactcttag gtaataaaat gcactttggt
2401 gcttataaag gaaaataatc atcacaggta gaagaggagg aaggcaagac

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Exon 1

Exon 2

2451 taggttttga ttcaaaatgt tttctgtttt gctaggaagt ctagaaggaa
 2501 tttggtcaaa tgacctgagg aggcaggag atttctccca gtggcacatg
 2551 gcagtccaca agaagactag gggcaggaa acaaagcaag attgtatctg
 2601 atttctacag gactccaaca ctaccctgcc aatacccttt tctcctctga
 2651 aagccatgat cccaaagggt tccatttctt ccgggttttt cacattctac
 2701 caacaagcag aatgtcttcc ccactgacag ctcaacagtt gagttttctg
 2751 gggttctacc ccttcatcaa cacagccttt gctttcctgg ttactgagta
 2801 aataaaacac actggccact tctgcttagc cttcaggagc cactctggct
 2851 ccaccctgaa gtccatttcc ctccaagaac taagacattt ggagattctg
 2901 cctaaaatat gcttaataaa aagggataaa ctgtctctca ctttctttcc
 2951 cccacagctt gtcttaagaa caacggtgta accatttagt aaaaatcctt
 3001 tcaggctagt aaaatgtaaa aagagaagag gtatcgggta acaacaatg
 3051 aaaataaaat cattcagtgg tagaaacat agccacact gtcactaaga
 3101 actgtcctcc agcttacatt aatcaaaata agccacact gtcactaaga
 3151 catcttgacg taagaagcca ttcaccctct cattgcaatt agtgtcataa
 3201 agctgaatag acaggtcaga aatgaaaatc ataggccaat taagttattc
 3251 tcatttttcc acctccagct agctcttttt gagaattttg attttaatag
 3301 ataataaaac agtatgctaa ttgggtgggtg ctgagcctga agccgtgaac
 3351 tgaaggaaac ttcaacaaac atttggtctag ggcctgctct aagcagaggg
 3401 gctacgacaa tgggttaaggc atttctctag aaaccagcac tcagcagaat
 3451 ttctggcacg agattttgtg agttttctag tgggtgtgtct tatctttccc
 3501 caatagatta taaactcctc gaggttgaca gaacacattg ctgatcttta
 3551 tatcctgcat gtttatggta ttcggtagac atttataaaa tgaattcatg
 3601 aaaagcagaa catctagaaa tgaagtcaac attgcagaga agttagctat
 3651 atgaaacttt gtaaataccc tcaaggaaag aggaagaagc agattttctg
 3701 gaaatcaagg gacctcccag tataagagca attccttttg tccaaagaag
 3751 ggcagctata agaacagaga cataactcct ccgtaagaaa agataaaaat
 3801 tctgaaagtt ctctaagaac atgcccagcc ctgacctgcc tctcactctc
 3851 agtagcatgg aagccgtact atctcttctc ttgacacaag catccacttc
 3901 aatcccacagg acaaatatca ccaatatgag aagataagat ctgttttata
 3951 gtcaacttgg ctgacatgta ctaattttctc aaggtcagga tagctctcta
 4001 aatagaaata cttgtttgtt ttaaggaatt ttatttaaat ttgtgtatct
 4051 taaattttta ttttgatctc ggctcactgc aacctccacc tcccagggtc
 4101 aagcaattct cctgcctcag cctcctgagt agctgggatt acaggcacct
 4151 gtcaccatgc ctggccaatt tttgtatttt tagtagagac cggattttac
 4201 catgttaacc aggctggtct caaactcctg acctcaagt atctgcttac
 4251 caaggtctcc cagagtgtcg agattacggg catgaaccac tgctcccagc
 4301 ctcatgtagt tcttaagagg aagaaaagcc tatagattag tgagaagtag
 4351 acaaattagc aatttgaatc aaatgaaaac ttggtttgat ttcattcat
 4401 ttggagacac tttcgggtgt tccattttga tctgattcag gacactgatc
 4451 ttcgattcta agttgcactg gtttaattgt gattatttta caaaatcata
 4501 acagaataca tatctgggtc cagttcaagg tacagcaagc cattttcaat
 4551 gtttccagct tgggtgtttat gattcataca tgaatcattt gggcatgcag
 4601 acacacccaa atagaaacct caaaccattt aaggtataaa taggttttagg
 4651 atgggggagg atggacaaca aaaaaaacct cagtaaggct cctccacaaa
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 5201 tgggataaat gaacattgtt atttaggtat ggttaaatga attacttttc
 5251 agggagcagat ttatatatta acaggtgtga aaaacttgaa tggataaatc
 5301 atttataaag aaatttcagg aatcaactaa tcccaagggg aaagacccac
 5351 taagacacta gattttgctg gagctactca aacaaattca tctatcat
 5401 ctacctaaag cttccaatca atgagactag ccgcagtgac actgtctgtc
 5451 aaaactacct cagtcatttt ttccaaggc aggaagcatc cataccctt
 5501 cacaccttaa tctaatttcc cctatctcca cccactccc acttctatga
 5551 ccccttccc cccataccca ccccggaagc atctactagc caacttagtg

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FIGURE 1C

5601 aagttctgtc acgctctcac aaccacctct gtgcagcaat gattctgtaa
 5651 atatccatgt gtcctcaaca ccagggtcaaa ttagtccctt tggtaaaaaac
 5701 attcattccc tcaaattctc ttccaatata ctaatatacc ttcccaaaaa
 5751 gtaaggagaa gcttgaaagc tagctggatt gatgatggta tgtgatgttc
 5801 tataagttat agttagtaag catgttttta ggatattttt ctgctctcca
 5851 aagagacaca attccggaag atatttactt ttgtgtattt ccacattttg
 5901 gtttaagttt ggagccatct ctagatctta atttcattcc cctaataatgt
 5951 gttatactag tagaattttc caaattacat agaattataa ctgcaactct
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 6051 ttctttccct gcagggatta tgtaaagagg catgttgacc tgctagccct
 6101 atgttacttt aagtatatgc acacacacaa aaaggaacaa aaacagctgg
 6151 gaattgatta tgttgatatt ctgaataaaa gcaatagtcc taattatgta
 6201 tgtctaatta gccacagctc ttcaagaatt gctgcaaatg tcacagggtt
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 6601 gttaatatgg attggtattc tcaatacata ttgtagataa aattcaagac
 6651 tagctctacc actgcctctt ttcttttttt tttttttttt ttatttgaga
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 6751 tcactgcaag ctccgcctcc cgggttcacg ccattctcct gcctcagcct
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 6951 tacagggtgtg aaccaccgag cccggccacc actgcctctt aggcctctta
 7001 atttctttat catttaagaa gaataagaaa atgcttctat gttttaccaa
 7051 aattctgtga ggacaaatga ggaaccattg taactcctac aaggtgagtg
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 7151 gccaaagctc taggggctta aataaggaag gacaggacca ttgttaataa
 7201 catcaagttt ccactacagc ttctctccaa acaagtcaaa tattctgaat
 7251 attattcact aatctcttta gctgccattt cagtaaatag cgagcatttt
 7301 atttcaacta aaaccaagca agagaaaatg aactgcttta tctgaggtta
 7351 cagcagcaaa ggcaccagaa cttgtctcat ggcttaccga gcaagggtca
 7401 gaagaaccat ccctaattta aatcatctcg actgaatgta acagattttt
 7451 gtattttcaa ctcatatgaa aataaaacaa tgagacctca tccaaagggt
 7501 gatttagaga gtacctctaa acaaaacaca gtgaaaatag acccagcatc
 7551 tggatttgaa gaacacattt cctcttacga gtctatccca ttgtctagat
 7601 tgctggcaat ggctttttta aatttaaat gttattgaga taattgtaga
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 7701 caatttccgc aaaaggtaac attttgtaaa actatagtat aatatcacia
 7751 ccaggataat aatattgata cagctcacaa atctcattca gattttctca
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 7901 aaacaacaat caagatattg gacagttccg gccgggcacg gtggctcact
 7951 cctgtaatcc cagcactttg ggaggccgag gcaggcagat cagcagggtca
 8001 ggagatcaag accatcctgg ctaacacggg gaaaccacgt ctctactaaa
 8051 aatgcaaaaa attagctggg cgtgggtggg ggcgcctgta gtcccagcta
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 8151 cagtggagcg agatcgcacc actgcactcc attctgggca acagcgcgag
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 8251 tcacaaggat ctctcaagtt accccttgct aaccacatcc accttctcct
 8301 tcacacttgc acaccccttc ccttctccag cctgacccca gcagccacta
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 8451 ataattccct ggcaattcat ttatgttact ctgtgtatca atagttcatt
 8501 catttttatt attgagtagc attccatggg atggaggcac cagagcttgt
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 8601 attatgaata ctcttctgt gaacattcat gtacaggttt ttgtacaaac
 8651 ataagtttcc atgtctctga cacgaatgcc caagagtaca attgctgagt
 8701 catatggtaa ctatatgtcc agttttataa gaaacgacca tgctcagaag

D6S280

FIGURE 1D

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8751 gaccatactg ttttacattc ccatcagcag tgtttgaatg atccagcttc
8801 tccgcatcct cccagcatt ttgtgtgtc actatTTTTT gccactatTT
8851 tttatttttag ccattctgct agctgtgtag tgataccatt gcgatctaatt
8901 ttgcattttt ctgatggcta atgatgtcaa ataaactttt atgtgcttct
8951 ttgccatatg tgtaacttct tttatgtatg tectctttta tgaatatcct
9001 atttatacct ttgccaattt tctaattgag tttttggttt tttactgttg
9051 agtttttaagg tttctttaca tatttttagat attagtcctt tgcagatat
9101 gtgggtttaca aacattttct cccagtctat ggcttgcctt ttcacctta
9151 gtacctgggc tctcacagag taagttttta cttttgatgg agtccaattt
9201 ctcatTTTTT ccttttataa cttctgcttt tgatgtcaag attaagaact
9251 ctttgcttag tccaaatccc aaaaatatct ccattTTTTT cctaaaagtt
9301 ttattatttt atgtttaatt tttaaacctg tggctcattt ttaaagtatt
9351 atcataagat aggaagtata gattaaggtc cactTTTTTg cctatagatg
9401 tccaattttt ccagcatcat ttgttgaggg ccttctctcc tccattgaaa
9451 tgcttttgca cctttaaaac aaatcaattg agcatatttg tgtgggtcta
9501 gttctgaatt ctctattctg ttcactgttc tatatgtctg tatgttccat
9551 atgtctatcc ctccaccaat ccacagtctt gattactgga gctataatag
9601 taggctttaa tatcaggtaa agtgattgat ctggttttat tcttctttgt
9651 cagcattggt ttagctattc caggtcctgt gcatttccat ataaatttta
9701 aaataagttt gtatctaccc cccaaaaaaa actttgctga gattttgaca
9751 ggaattttat tagacctgta gatcaatttg ggaagaattg acatctttgc
9801 tatgatcagt cttccaattc ataaacacgg tatttctcct cactatttta
9851 ggtcttttct gatttctttt atctgcattt cataatctca atgcacataa
9901 accgtatgtg tttttctaag tggatattta agttattttt atttggaaatt
9951 attataaata ataattttgt gtttctaatt ttcatttcca catgatcatt
10001 gttagtataa agaaatatga ttaattttta tattgatcat acatcgtgca
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10101 tttttctgta gaccatcatg ccatttghta atagagacca ttttatgttt
10151 acctttccaa actgcatggg ttttttctt ttatttggct tattgcagca
10201 actattaata taacttacia tactatgttg aataagagtg atgaaagtat
10251 acatcttggt tgttcttaat gttggggaaa agcattcagt cttcactat
10301 taagtatgat gttaaagttg ttgtaaatgc tatttatcga attaaactgt
10351 taaacctctt ttcctaactt gccaaagatt ttttttaac ataaatgggt
10401 gttggatttt gtcaaatgct atttcgtcat caatttatgt gattttttt
10451 tagctttatt atataatgca ttatattgat tgatttcaac cattgagcta
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10551 ctgtttgcta atattttgct gaggattttt tgtgtctaag tttatgataa
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10651 tttgtgtgca ggataatact gacttcataa aatcattgag aaagtttttt
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Exon 3(D)

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FIGURE 1G

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FIGURE 1H

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24351 acacctttca gcagaaactc tataagccag cagagattga ggacctatat
24401 tcagcattat taaagaaaag aaattccaaa caagaatttc atatccagcc
24451 aaactaagct tcataaatga aggagaaata agattctttt caggcgagca

```

FIGURE 11

24501 aatgctaagg gaattcatta ccatcagacc tgccttataa gaggtcctaa
 24551 agagagtgtt aaatatggaa aggaagattt attactggca actacaaaaa
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 24651 atctgcataa taaccaatta acaacacaaa acaggatttg atccttcaaa
 24701 tccacacata tcaatattaa ccttaaatgt aaatgggcta aatgccaat
 24751 taaaaggcac agagtggcaa gttggacaaa gaagcaagac ccaacagtat
 24801 gctgtcttga atagacccat ttcacatgca gtgacgcaca taggatcaaa
 24851 ctaaagggat ggagaaaaat ctaccaagca aatgggaaaac agaaaaaagc
 24901 aggagtgtgt attctacatt caaacaaaaac agactttaaa ccaacaaaaa
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 27351 cctacctcc tgtgagagtc tgaagqacac tattgccaga gctctgccc
 27401 tctggaatga aqaagtattt ccccaatca aggaqgggaa atgggtactg
 27451 actgcagccc atggcaacag cctctggggc actgacaacc atctgaaggg
 27501 tctctctgaa gaggtctatc tggagctgaa cctgccaaact ggcattctca
 27551 ttgtctatga attggacaaq aactggaagc ccatcaagcc cagccaccc
 27601 agttcctagg ggaatgaagq accatgtgca aagccatgga agttgtggt

Phosphoglycerate
mutase,
processed
pseudogene

FIGURE 1J

27651 gcccaggcca aagccaagaa gtgaaggcca gcaaacaggc accctccctg
 27701 cccattgcat ccatctgtcc ctccctcctg aacatgtcac actgaccaca
 27751 tctatagaca tcttgagttg cagctgcaga tggggaccgg tggtcccat
 27801 tttcatttta gccattttgt cttctgcacc cactcccttc atacattcta
 27851 gtcagaatag cacttctagg gcacaggttc tcagtctaag ctgtggaaaa
 27901 gcccccgtaa tccaagagag ttcaaagata gtgacttggg tttttgcaag
 27951 tgctttgttt actaaggact tgtgaggagg agccatgctg agctacgacc
 28001 aatgaggaga agcaagagag cctgtctgcc cccaggagct agtcctgtgc
 28051 ttgtctgtag tcaggccact gcctgggggc tctagtcac ccagtggag
 28101 atgaatgtaa cctgcatggt gatgtgacag ctgtttcctc cctgacccca
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 28251 acaaaacaat aacccttcta aggtttctc gtggtggttg aaatagtccc
 28301 acatgtgggc atcagaacat aagccattcc tcataccaat atggggtaag
 28351 ctccctgacc tttgaggggc aggagtgtt catgctgtgt gttttagaat
 28401 cctccctgc cttgtttcat ggcagtgaat tgcctcttgg tctctccaa
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 29351 cagctaacca ggtaggtgaa agatctctac aacaagcatt ataaaacact
 29401 gctcaaagta atctgagatg atataaaca aaggaaaagc attccatgct
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 29551 tagaaaaaaa aattatttaa aaatttgtat gaaacaaaa aaaagcctga
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 30751 agaaaaagga atgcttatat actgctggtg ggaatgtaaa ttagttcagc
 30801 cgtgtgggaa agccgtttg caatttctca aagaactcaa aatggaatta

FIGURE 1K

30851 ccatttgacc cagtaatctc actattgggt ttattctcaa aggaatgtaa
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30951 tcacaatagc aaagacatga aatcaaccta catgcccatt gatgggtgat
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31101 cattcaccta agcgaactga cacaggaaca gaaaaccaa tacacatgtt
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37001 ggccataacg gacaagtagt tctgcccctc aaatagtgct cctcacctat
37051 ccccagtggt atttcccag cttagtaaat agcactttat tcactctgatt
37101 gcttagacca aaaaccctga agtcagcctt agactccctc gtttgtctca

FIGURE 1M

37151 tcccacagtc agtccttcag caagtcttgg cctctccacc ttcacaatgt
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FIGURE 1P

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Exon 4(A)

Exon 5(B)

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FIGURE 1R

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FIGURE 1U

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FIGURE 1W

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FIGURE 1X

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Exon 6(E)


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Exon 7(C)

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92051 gcactccagc ctgggcaaca gagtgaagt ccatctcaaa ataaataaat
92101 aataaaataa aataaaataa aagaagttct gatgtggtgc aatatgttta
92151 acagccagct gaaaatgcca aagtagcctt ctctctcctt tgggtattta
92201 tcagggctaa gtataaggag caaaagattc ttcatgtgta gtaacttaat
92251 catttctctt tttattttat tctaaatcct gctctctttt ttctttttca
92301 tgtcccccac tatgccacat gcagTGTGTT TGGCGTAGTT ACGCAGCTGA
92351 TGAGAAATCT GTTTCATTG CAACCTGGAA GCCACACTTG AAGGCCCTGC
92401 ACACCTGCAG CCTACCAAG taggtatcag tgtgacagct gccactgtag
92451 ttgagtcttt tcaagtctgt taaacaaacc ataccacac acacaaaaaa
92501 aggtgttaat gtttggcttc tcttattctc tgttgctcct agagagattc
92551 aaacctatct agtagcagtt ctggcacaaa actaaatgga atcagtatca
92601 ttccctcaca tccacagact ggggttaaag attaaataa tgtaaatttt
92651 atagagattt atttttacta ttcatgctt actttcta atgtctcattc
92701 gtaaaagcca ccagcatcct aaaggtatgc accacagttc ttgaaaaaca
92751 aggattatct attttgcacc catcgcttga ccccaagaga tgagtgttta
92801 gagagtaatc catctttgta cgtttagatc tctcaaagcc atttctcatc
92851 tggatcctct ctggatggc ctcaaagctt tacttgaga tcaaaactac
92901 atcagtgcca aaaaaagaga aaaataggag tcctaatagg attatagttt
92951 acaatgagga aatgggaccc agcggattaa aatttggaat ttgcattcac
93001 aattttaaag taagactact tttcttcaca ttcatgtgc caaagtaaat
93051 cactcagcca tgcttaaat caaagaaaat ggggaagtac aattttacct
93101 tttaccatgt gcctagaagc aggcaagaac caaggacatt atggacagtc
93151 ctaatgatta ccacagagat ctgtaattaa aaaaaaa aagggcttag
93201 tcttgagtc ttggaacctt ggaactcag tcaactatca cagaaaatgt
93251 taaatcatat tcaccaccta attaaagaag tcctcattga aataccgaag
93301 cagtaagtca tgagaaggc tttctgtgag tcaccagctt tgattagcgt
93351 agtcagttcc tcagggtgtt caaaagtatt taaattgctc atccgacatt
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93451 tggcttcag ggattcggga cacctaacta ctgtgactca caaaaaacca
93501 cctgttcgta ctgatcttg gagatatcag ctgaggaaac ctccatgaca
93551 ttccctggca gtaccgtctt aatggaggtt tgtgatgcag cagaatgcat
93601 accattggga agcaccagat ccatcattaa ctacattact tccctgttct
93651 gcccttggcc tcagttttcc caccacaaa gagaaaggca agagttgggc
93701 aagatgattc ctaagctcta atgggaaatg cctcctgggt ggtggtatct
93751 aaaattcttg tcagcaccta ggacagagat attcatagca ctccagggat
93801 ttcagagagg atggaacctt agcatggata gaagcatgga tgctgttga

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Exon 8

FIGURE 1AE

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93851  tgcattgtttg gattaaaaatc ctcttttcat ttagatcttg aagtttagtt
93901  gaacttttta tggagtttaa gaccctttca acattttgat atcaaaaaac
93951  cgaaaaataga acctaactcc tgtgccattt attccttggg agtatgaacc
94001  aaaaaataaaa attatataga aattgtattt cttgtcttca tgaagtttgc
94051  taggtaaaatg taaaaaggga atctgagtag gaaaactgat agagaattct
94101  caagtgcagag aggagagtgg tctattatca tatgtgatta tttggcttcc
94151  cacttactgc agtttttggg ttaaaagtca ttaaaagcct ggaaaaactg
94201  ttttaataatg agtcaaattc ccccagtaaa tcaactatta ttttattcac
94251  ataagttctt tctactcttc tgatattttc cctgtcttaa gtgggggtgg
94301  aggtggagga ggatttatgc aaacacctgt gttctctatg tctactgtg
94351  cctttccctc actttccttt tcttgcaaac tcatgaacca tggggctcag
94401  ctccattgaa tgaagaacag ttatttgtcc agaatgacac agcagtcact
94451  ggtaaagtgc atgggaaact agatgtccta acatctctcc ccttccagtg
94501  atgcttcatt gcttcaaaat gcagagggtt ttaatccttg ttgatgtttt
94551  ttgttaaacc attgagaatg tgatggaaat tatggggtct tttcccaaga
94601  agtaaatcaa tgcacagaga aatcaatact ttgcctacaa ttttaattgt
94651  ttacacagag cctgaagcc aagttcaaac ttttgtttta caaagcaaac
94701  ttgctttaat caagtgcaca taattttcag tgacttagag ggatcttttt
94751  acatttaagt ggcttaccga atggagagtg ttgtagttag aaacagacta
94801  caattactat tttatttaca ttgtgtattt tccttttagc ttcagcctaa
94851  gaacttctga tgggaaagat catttattca gtcattgtat cattcaacaa
94901  ttactcattg agcacctatg atgtgcaagg catagtctta ggcactgaga
94951  atgaagcagt tggagtaaaa aaaaaaaaaa agttagaatc tctggccttg
95001  ggaagtatgt attcaaggga tgttgggata gacaatataa ataaataaat
95051  ataggatatg ttagatggca ttaagtgtca aggagaaaaa taaaataaag
95101  aaggaattta gggagcatca gaggctataa tttcaaatag gtggccaggg
95151  ggaagatcaa tttatcaaca atatcatcat catcatcatc aatgttactg
95201  ttatcattaa aaaacaccag ccccatgctc ttgttcccca gttttaaaga
95251  catagtggga tgctttgatt ccactaaaca ggatgaaaga gaggtctaag
95301  aaacagctgt gcagggcaga gagaatggg aggagggaca ctcaaacctg
95351  ccagggatac aaccagcagt tccttactct ctcttttcag gtctgttttg
95401  tctcttacct acacttttaga ggtcttagca attctatttc aaagttttat
95451  tttataaaca gaaggatgta tagaagcaag tacttttctt gattttctcc
95501  tcaaagagag tgaagctgca aagggcacaa cacaggtaaa tatgtctattt
95551  agggaatgag tcagaaattt tatgaggcta tggggaatta tcaagctcca
95601  aaaacacctt gtgggtacct aagaagtggg gatttggaga ttatctaacc
95651  taaagccttt gatttactca taagaaaacc aaaacctgca agcaataaag
95701  gtgctgccc aaaggcacac agctcgtttg caaagagtac agacctaca
95751  ccatggtgct tagacctaca tttgctazaa tgagttatta caaatgccac
95801  ccaacagtat aggtctaaaag agttttggta aatattctat gtaccttatt
95851  tactccaagg aaattttgat tttatacgt acaaaaaaaaa atctgcctca
95901  gcaagtgact gagatacaat tcattaatga atccagggtt agaaaccaa
95951  gtctgccaga tgcacagaga acagttatgt tgtaactagc aacattctaa
96001  gagcccttgc taattctggt tagatcagaa ccacttttct ttagccattg
96051  atagcttttg ctaatgaaaa gtctattgtt ttttattcta tgtgggcagt
96101  cttggctttg ccaagtaaat gttgtgctat ctctggtctg tatcacaaag
96151  aatataatgt agcaagttga gtacatttat tataaagaac actgcttttg
96201  tggatcttgc atgaaaagag ttacttaagg tatttgattc cccaatctcc
96251  aatttggcca ttatcaagt ctataaatat attcactggt ttatcatcat
96301  ttctcttctg cctgcacgca cctgaagGAA AGAACAAGGG GAAGCATCAA
96351  GCAGgtttgt gatttctctc ttgctacatg tttgtttata aatctgatac
96401  ctaccagggt ttttaattgt gtctcatgtg agtaaaatcg atcaacaaat
96451  acaagatgat taaaagtgc ctttcacaag attgcctgca aagattgcta
96501  ttttattgat atttcgccc ttagtatcaa agtgcctttc cctaactcac
96551  tcctgctttt ttcaaaatct gcagggcatg gaacatttgg aggtggggga
96601  ggaggggaac tgatcttggg ttagtccttg ctgttgtttt cccagacaga
96651  agtcttatca aagtattcaa atatggtaat ctagagaatg aaagaaagaa
96701  attttttttc tgaatgtaaa aagtccaggc agcagcttag gatacactcc
96751  ccttcactag ggtccttctt ttggagtgt atatatatat atatatatat
96801  atatatatat atatatatat atacacacat atatatatac
96851  tatacatata cacatacata cattatatgt atatgtatat atacctatac
96901  atataatctt ttttttttgg caagatgaaa ccacctctct gtgacatctc
96951  cagatctcca gccactgag tgctgaggtc tactcaagt actcaaagag

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Exon 9

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97001 ccccatcccc atcttttagg aagaagacaa cctcccaaa aattcccaaa
97051 ataatttatt atcagcttcc catgacttag atggaatgcg tcgtcagatt
97101 acagcagaga attaaaccta gaggaatac gaggtgaaag aaaaatttct
97151 tgactctgtg taatgagtag caggaagtgc ctgatttga gagcaaagcc
97201 ctgaaaaaca gagccagggtg gaaccagta ttaatgatgt gaagagtggc
97251 agaggcagaa ccagcaagga gaatcccagg tgcttggaaa ggaagaagag
97301 atacattttt ttctctatca ttgtcactgt gtttccataa agaaatgaag
97351 gcatccacct acccagagtt ggtccctaag tggaggccag tgtgggcca
97401 gggattgttc ttttagctta gtactattat aataattata ttaataataa
97451 tataattatg caatactgaa gccagttttg aaagttcact tgggtgatta
97501 aggctctgga ttatccattt ttgcattatg tttatatgta aagataaaca
97551 aatgaaaaca taaatgcatt cgtctatgat gggagatagg cacgatagga
97601 tataacaacat caggcacatc ttctgcgtag gtaacctacc caagggatgg
97651 cattaagatt ctttctctta tttggtagca tagagttaga gccaaaggca
97701 ttggatattc cttggagata tttccagaaa aaagtcattc ttccccacct
97751 aagaaaacgtt ttgacccaaa gagaggttct agtcattaga ttcggaaatag
97801 tctttgccta gacactggaa gagacaagct gaccaattct agacttttag
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97901 tttacttgaa aaaagttaca caaaataaat catagccatt ttaaggtagc
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98101 catcttagtt tcatcctcca aaacggagct gttaacacct aaaagagaag
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100001 tcagttcttt ttggtacatt caggtacaaa ttactgttag tctcaactga
100051 gcctgtgttt ttttctctta ctccaatcat aaaatacttc tttagcatca
100101 tttaatcact catttctttt cctctgaatt cccactaaaa cagtactaat

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FIGURE 1AG

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100151 ctcatatatg tgggtggtaaa tgtgtttatt gatttcattc tattaaaaaa
100201 ttagttggaa aagtcatttt taaaatggga caagtttttt tctgttttga
100251 tataaattgt cattttcaga gaactgaatt tacctctgaa tccatctgtc
100301 cagaataagc caatattctc accttgaggt tttatgtggt tctcccttcc
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100701 cttgtgctgt gagccaccga gtgctttttc tgaaccactc ctgtgtgggt
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100951 aacatagtca acttggtgcc ttattggcaa aatgttccat tgtttcaaaa
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101151 gttttgttga acatatattc tatctgacaa ttggttacct atatcaacta
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101751 tgcagacca ggttacaccg ccacccacc tgagccctgt tcagagactc
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103151 tgtatttagt tgacatagaa aagagatata tcttgaagat tggagaaaa
103201 aatttgatat taactaaaac caacctttta tagtaattag catctgttag
103251 ttccagaaaa ggtaatatag aaaatcaaat atagttagga ccaattgtaa

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FIGURE 1AH

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103301 tgatatctat gtcaacttga gctattcatt aatctgaata aaggtgcaga
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103401 cagatgtgtt gaaactaaaa agagatttga aacttttaca atttaaaaaa
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Exon 10

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118901 agtaaaacag aacttgtttt aaactctagt tccccacta ggttgggtga
118951 gatgagacaa acgacttaac ctactgcca ctttaatttg ttctctctct
119001 ctcttttaggg tggtagaat gataacctacc taatagggtt acgtgagtaa

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FIGURE 1AM

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119051 taataagata taatgtgtgt aaaattcttg tacaatgccc agcacagaat
119101 aggtgctcaa tatattaaat atattgttat tatttattaa ttaattaatg
119151 ctgatttctg cattaatatt gactaattga aatcctggac ttgcttaatt
119201 tgcattgtatt tgtcttccct tcttcagta cttgatggca atttctacct
119251 gtggtaaatg gaacgttaaa agttatatgc ttatacaaac tttagtcctt
119301 tattccttgg agtgagtttt aagagtcctc atgttgaata attcatgtaa
119351 tcacagaaat aatactatgt atcagggacc gcttccttta ttaaagataa
119401 aggcagtggg aatactgcct ttgtcagaaa tacttcagtt actctgagag
119451 agagagacat ttgtttacta tatgacagca cagtgcattg caaataatag
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120751 gccaaaaata atttgatgca tgacttttcc cccagagtt tcttattata
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120951 CAATATCTCG CTGGTCATCT GGACATGTTG TGTAGAATTA AAAGCCTTCA
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```

Exon 11

Exon 12

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122351 ataactctgt ctattaatgt aagatctcta tagttatgat ttttgctata
122401 ttttgaaatg gttaaattca ggaactgcct gatcagagg agaaacatat
122451 tactttgtag tttaggacac tttacttcc agaagatcac ccataagtga
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122601 cataaattga agataactgt atttaatttt tttttccaaa actcttcatt
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122801 CAGTATGCTC GGTCTGGTGG TCAAGGTTGA AAAACAGgta caactcaact
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122901 gcaattgtat gtattccagt gattatttta aaataaataa aatcacaana
122951 agagtgaata aaattaaatt ttctttgtgt gtagacagt ctctctgaaa
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124201 AAGGAAAATG TTCAGGTTGC ACAGTCAAT CTCACCAAGG ACCGTTCTAT
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124851 TAATGTACCT TGAGTTAAAA AGCCTGAGAA ACCAAACACA GCTAATGCTA
124901 TGGGGTGTAT GAATATGTCA AGTTTAGGTC ATTTAGAAGA TTTGACACTG
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125101 ATTGGGGAAT AATAGAAATG GCTGCTTATT TCAAGATATA TTTGCCAACC
125151 CATTCCTATT CAGTCATTTT ATTATTAATG TAATTTGAAT GTCAATTTGT
125201 GTGCTTTTGG TGATTTAGCG CTGTGGCAAG CAATTTTGCA CATCATTTTC
125251 ATGTTGTTCT TTATGACAAG AATGTTCTTC AATTAGAAAA TGTGCAATA
125301 ATGAAATCA GGGCCAGTGA GGCAAATAGA CTATCTGACA TATTGAGCTT

Exon 13

Exon 14

125351 TATGAAAACA TATTGGCTGA TGGCAGAATC AACTTTATAA GTGGTCAACT
125401 TCTACACAAG CGTATGAAAT ACTGGTCAGT AGAACAGCCA TTGTGATTGG
125451 ACTGGTTTCT CTGCAATGGC GCCAAGCCCA GGCTTGCCAA TACTGCCTAT
125501 GTAAAGGGCA AGTGTGAGAA GCTATTCTCA TTTCGCTGAC ATACAGGTAG
125551 GACTATGGGG GATGGGACAT TTGAGTGGGA CTGAGATAGG AAAGGCTTGA
125601 AAAGAACCCA GAAACACCAC CAGGAAGTTG GCAAAGTAAA AGAAAATGAC
125651 TTCCCCCTCA AAGGGCAATG AGAGGGAGAG AACCAAACCA AAATAGAAGA
125701 ACTAGACTTT TTAGAAAATG AGTATTGCTA GGGGAATTCAA CTACCTAATC
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125801 TTAATATGCC CTGAATGTCT TTGCTATTA TGTGTACATT TTGCATATGA
125851 AAGTCTAAAA CGAAGCTTCC TTACTTTTT ATACTGTAGT GAAAATTTTC
125901 TATTCTTCCC AAGAATGTTG TCCCAAATCT GAAATTACTG GTTCAATTTT
125951 CTGATATAAA

KCN6q cDNA

1 CTGGAGTGAGGCGCGGGAAGATGCCTGGTCTTGCCTCGCGGACTTGGCA 50
51 GCCGCGTCCTGCGGGTCTGTCCACTGAACTGCTGAGGACTGCGGCGGTGG 100
101 CCTGAGGGAGAGCCGCCGGGCAAGCAGGGGGCCCGGATGAGCCTGTGG 150
1 M S L L G 5
151 GGAAGCCGCTCTCTTACACGAGTAGCCAGAGCTGCCGGCGCAACGTCAAG 200
6 K P L S Y T S S Q S C R R N V K 21
201 TACCGGCGGGTGCAGAACTACCTGTACAACGTGCTGGAGAGACCCCGCGG 250
22 Y R R V Q N Y L Y N V L E R P R G 38
251 CTGGGCGTTTCATCTACCACGCTTTCGTTTTCTCCTTGTCTTTGGTTGCT 300
39 W A F I Y H A F V F L L V F G C L 55
301 TGATTTTGTGAGTGTCTTCTACCATCCCTGAGCACACAAAATTGGCCTCA 350
56 I L S V F S T I P E H T K L A S 71
351 AGTTGCCTCTTGATCCTGGAGTTCGTGATGATTGTCGTCTTTGGTTTGG 400
72 S C L L I L E F V M I V V F G L E 88
401 GTTCATCATTCGAATCTGGTCTGCGGGTGTGCTGTTGTGATATAGAGGAT 450
89 F I I R I W S A G C C C R Y R G W 105
451 GGCAAGGAAGACTGAGGTTTGCTCGAAAGCCCTTCTGTGTTATAGATACC 500
106 Q G R L R F A R K P F C V I D T 121
501 ATTGTTCTTATCGCTCAATAGCAGTTGTTTCTGCAAAAACCTCAGGGTAA 550
122 I V L I A S I A V V S A K T Q G N 138
551 TATTTTTGCCACGTCTGCACTCAGAAGTCTCCGTTTCCTACAGATCCTCC 600
139 I F A T S A L R S L R F L Q I L R 155
601 GCATGGTGGCATGGACCGAAGGGGAGGCACTTGGAATTAAGTGGTTCA 650
156 M V R M D R R G G T W K L L G S 171
651 GTGGTTTATGCTCACAGCAAGGAATTAATCACAGCTTGGTACATAGGAT 700
172 V V Y A H S K E L I T A W Y I G F 188
701 TTTGGTTCTTATTTTTCTGCTCTTCTGCTATCTGGTGGAAAAGGATG 750
189 L V L I F S S F L V Y L V E K D A 205
751 CCAATAAAGAGTTTTCTACATATGCAGATGCTCTCTGGTGGGGCACAATT 800

206	N K E F S T Y A D A L W W G T I	221
801	ACATTGACA [•] ACTATTGGCTATGGAGACAAA [•] ACTCCCCTAACTTGGCTGGG [•]	850
222	T L T T I G Y G D K T P L T W L G	238
851	AAGATTGCTTTCTGCAGGCTTTGCACTCCTTGGCATTCTTTCTTTGCAC [•]	900
239	R L L S A G F A L L G I S F F A L	255
901	TTCCTGCCGGCATTCTTGGCTCAGGTTTTCATTAAAAGTACAAGAACAA [•]	950
256	P A G I L G S G F A L K V Q E Q	271
951	CACCGCCAGAAACACTTTGAGAAAAGAAGGAACCCAGCTGCCAACCTCAT [•]	1000
272	H R Q K H F E K R R N P A A N L I	288
1001	TCAGTGTGTTTGGCGTAGTTACGCAGCTGATGAGAAATCTGTTTCCATTG [•]	1050
289	Q C V W R S Y A A D E K S V S I A	305
1051	CAACCTGGAAGCCACACTTGAAGGCCTTGACACACCTGCAGCCCTACCAAG [•]	1100
306	T W K P H L K A L H T C S P T K	321
1101	AAAGAACAAGGGGAAGCATCAAGCAGTCAGAAGCTAAGTTTAAAGGAGCG [•]	1150
322	K E Q G E A S S S Q K L S F K E R	338
1151	AGTGCGCATGGCTAGCCCCAGGGGCCAGAGTATTAAGAGCCGACAAGCCT [•]	1200
339	V R M A S P R G Q S I K S R Q A S	355
1201	CAGTAGGTGACAGGAGGTCCCCAAGCACCGACATCACAGCCGAGGGCAGT [•]	1250
356	V G D R R S P S T D I T A E G S	371
1251	CCCACCAAAGTGCAGAAGAGCTGGAGCTTCAACGACCGAACCCGCTTCCG [•]	1300
372	P T K V Q K S W S F N D R T R F R	388
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389	P S L R L K S S Q P K P V I D A D	405
1351	ACACAGCCCTTGGCACTGATGATGTATATGATGAAAAAGGATGCCAGTGT [•]	1400
406	T A L G T D D V Y D E K G C Q C	421
1401	GATGTATCAGTGGAAGACCTCACCCACCACTTAAAAGTGTATTGAGC [•]	1450
422	D V S V E D L T P P L K T V I R A	438
1451	TATCAGAATTATGAAATTTTCATGTTGCAAAACGGAAGTTTAAAGGAAACAT [•]	1500
439	I R I M K F H V A K R K F K E T L	455
1501	TACGTCCATATGATGTAAAAGATGTCATTGAACAATATTCTGCTGGTCAT [•]	1550
456	R P Y D V K D V I E Q Y S A G H	471

1551	CTGGACATGTTGTGTAGAATTAAAAGCCTTCAAACACGTGTTGATCAAAT	1600
472	L D M L C R I K S L Q T R V D Q I	488
1601	TCTTGGAAGGGCAAATCAGATCAGATAAGAAGAGCCGAGAGAAAATAA	1650
489	L G K G Q I T S D K K S R E K I T	505
1651	CAGCAGAACATGAGACCACAGACGATCTCAGTATGCTCGGTCGGGTGGTC	1700
506	A E H E T T D D L S M L G R V V	521
1701	AAGGTTGAAAAACAGGTACAGTCCATAGAATCCAAGCTGGACTGCCTACT	1750
522	K V E K Q V Q S I E S K L D C L L	538
1751	AGACATCTATCAACAGGTCCTTCGGAAAGGCTCTGCCTCAGCCCTCGCTT	1800
539	D I Y Q Q V L R K G S A S A L A L	555
1801	TGGCTTCATTCCAGATCCCACCTTTTGAATGTGAACAGACATCTGACTAT	1850
556	A S F Q I P P F E C E Q T S D Y	571
1851	CAAAGCCCTGTGGATAGCAAAGATCTTTCGGGTTCCGCACAAAACAGTGG	1900
572	Q S P V D S K D L S G S A Q N S G	588
1901	CTGCTTATCCAGATCAACTAGTGCCAACATCTCGAGAGGCCTGCAGTTCA	1950
589	C L S R S T S A N I S R G L Q F I	605
1951	TTCTGACGCCAAATGAGTTCAGTGGCCAGACTTTCTACGCGCTTAGCCCT	2000
606	L T P N E F S A Q T F Y A L S P	621
2001	ACTATGCACAGTCAAGCAACACAGGTGCCAATTAGTCAAAGCGATGGCTC	2050
622	T M H S Q A T Q V P I S Q S D G S	638
2051	AGCAGTGGCAGCCACCAACACCATTGCAAACCAATAAATACGGCACCCA	2100
639	A V A A T N T I A N Q I N T A P K	655
2101	AGCCAGCAGCCCCAACAACTTTACAGATCCCACCTCCTCTCCAGCCATC	2150
656	P A A P T T L Q I P P P L P A I	671
2151	AAGCATCTGCCCAGGCCAGAACTCTGCACCCTAACCTGCAGGCTTACA	2200
672	K H L P R P E T L H P N P A G L Q	688
2201	GGAAAGCATTCTGACGTCACCACCTGCCTTGTTCCTCCAAGGAAAATG	2250
689	E S I S D V T T C L V A S K E N V	705
2251	TTCAGGTTGCACAGTCAAATCTCACCAAGGACCGTTCTATGAGGAAAAGC	2300
706	Q V A Q S N L T K D R S M R K S	721
2301	TTTGACATGGGAGGAGAACTCTGTTGTCTGTCTGTCCCATGGTGCCGAA	2350

722 F D M G G E T L L S V C P M V P K 738

2351 GGACTTGGGCAAATCTTTGTCTGTGCAAACCTGATCAGGTCGACCGAGG 2400
739 D L G K S L S V Q N L I R S T E E 755

2401 AACTGAATATACAACCTTTCAGGGAGTGAGTCAAGTGCCTCCAGAGGCAGC 2450
756 L N I Q L S G S E S S A S R G S 771

2451 CAAGATTTTACCCCCAAATGGAGGGAATCCAAATGTTTATAACTGATGA 2500
772 Q D F Y P K W R E S K L F I T D E 788

2501 AGAGGTGGGTCCCGAAGAGACAGAGACAGACACTTTTGATGCCGCACCGC 2550
789 E V G P E E T E T D T F D A A P Q 805

2551 AGCCTGCCAGGGAAGCTGCCTTTGCATCAGACTCTCTAAGGACTGGAAGG 2600
806 P A R E A A F A S D S L R T G R 821

2601 TCACGATCATCTCAGAGCATTGTGAAGGCAGGAGAAAGTACAGATGCCCT 2650
822 S R S S Q S I C K A G E S T D A L 838

2651 CAGCTTGCCTCATGTCAAACCTGAAATAAGTTCTTCATTCTTTCCAGGC 2700
839 S L P H V K L K 846

2701 ATAGCAGTCTTTAGCCATACATATCATTGCATGAACATTTTCGAAAGCC 2750

2751 CTTCTAAAAAGTTGAAATTGCAAGAATCGGGAAGAACATGAAAGGCAGTT 2800

2801 TATAAGCCCGTTACCTTTTAATTGCATGAAAATGCATGTTTAGGGATGGC 2850

2851 TAAAATTTCCAAGGTGCATCGACATTAACCCACTCATTTAGTAATGTACCT 2900

2901 TGAGTTAAAAAGCCTGAGAAACCAAACACAGCTAATGCTATGGGGTGTAT 2950

2951 GAATATGTCAAGTTTAGGTCAATTAGAAGATTGACACTGTATTTTGAAA 3000

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3051 ATACAAACTACATTTTCAAGATTAGGCCATAATGTATATTAAACACAAT 3100

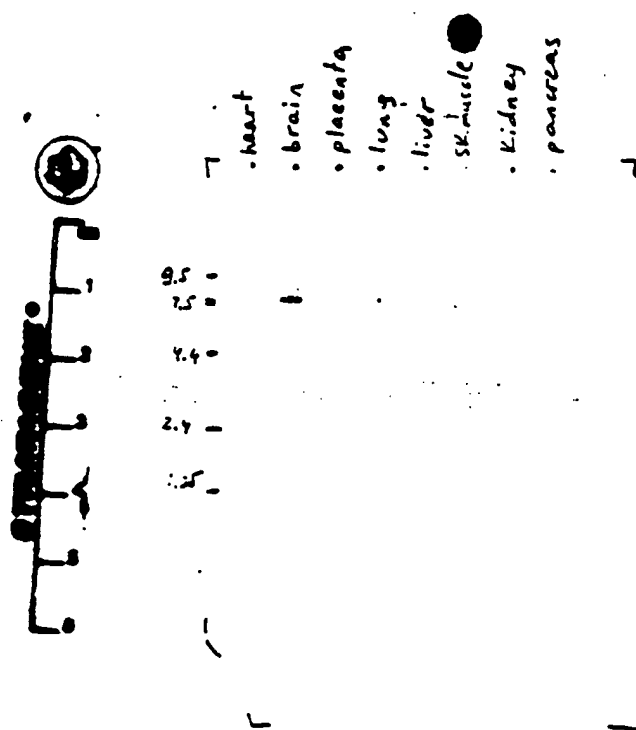
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3151 AATAGAAATGGCTGCTTATTTCAAGATATATTTGCCAACCCTTCCTATT 3200

3201 CAGTCATTTTATTATTAATGTAATTTGAATGTCAATTTGTGTGCTTTTGG 3250

3251 TGATTTAGCGCTGTGGCAAGCAATTTTGCACATCATTTTCATGTTGTTCT 3300
3301 TTATGACAAGAATGTTCTTCAATTAGAAAATGTGCAAATAATGAAATTCA 3350
3351 GGGCCAGTGAGGCAAATAGACTATCTGACATATTTGACTTTATGAAAACA 3400
3401 TATTGCCTGATGGCAGAATCAACTTCTATAAGTGGTCAACTTCTACACAAG 3450
3451 CGTATGAAATACTGGTCAGTAGAACAGCCATTGTGATTGGACTGGTTTCT 3500
3501 CTGCAATGGCGCCAACCCCAGGCTTGCCAATACTGCCTATGTAAAGGGCA 3550
3551 AGTGTGAGAAGCTATTCTCATTTCGCTGACATACAGGTAGGACTATGGGG 3600
3601 GATGGGACATTTGAGTGGGACTGAGATAGGAAAGGCTTGAAAAGAACCCA 3650
3651 GAAACACCACCAGGAAGTTGGCAAAGTAAAAGAAAATGACTTCCCCCTCA 3700
3701 AAGGGCAATGAGAGGGAG

FIGURE 3A



probe: DL/ER PCR fragment.

FIGURE 3B

RT-PCR analysis of the KCN6q gene expression in human tissues

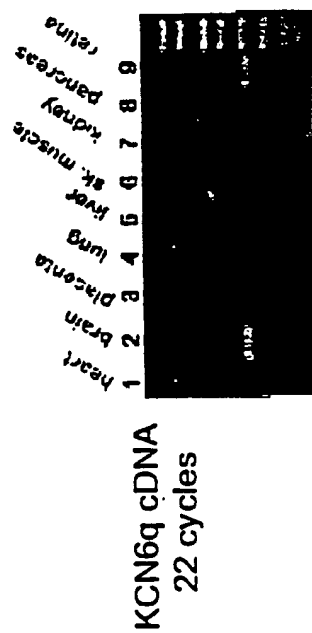


FIGURE 4A

KCN6q_MS.....LLGKPLS.....
 KCNQ4_ MAEAPPRRLGEGPPPGDAPRAEVAWAVQSEOGEGAGCGSPRRLLGLLGSPLPFGAPLPG
 consensus maeapprrlggpppgdapraeivaavqseogegaggs sprrlgllg pl pgaplp

KCN6q_ YTS.SQS.CR.RN...VK.YRRYQN...YINVLERPRGWAFYHAFVLLVFCCLMLSVFST
 KCNQ4_ PGSGSGSACGQRSAAAEKRYRRYQN...YINVLERPRGWAFYHAFVLLVFCCLMLSVLST
 consensus SgS SaC qR saa KRYRRYQNYLYNVLERPRGWAFYH FVLLVF CLILSV ST

KCN6q_ IPEHTKLASSCLLILLEVMIVVFGLFIRIRWSAGCCCRYRGWQGRREFARKPFCVIDTI
 KCNQ4_ IQEHQELANECLLILLEFVMIVVFGLEIRIRWSAGCCCRYRGWQGRREFARKPFCVIDPI
 consensus I EH LA CLLILEFVMIVVFGLEIRIRWSAGCCCRYRGWQGR REFARKPFCVID I

KCN6q_ VLASAVVSAKTOGNIFATSALRSRFLQILRMVRMDRRGCTWKLLGSVVYAHSKELIT
 KCNQ4_ VFYASAVVLAAGTOGNIFATSALRSRFLQILRMVRMDRRGCTWKLLGSVVYAHSKELIT
 consensus V IASIAV A TQGNIFATSALRSRFLQILRMVRMDRRGCTWKLLGSVVYAHSKELIT

KCN6q_ AWYIGFLVLIFSFLVYLVEKDANKFSTYADALWWGTITLTITIGYGDKTELTWLGRLS
 KCNQ4_ AWYIGFLVLIFSFLVYLVEKDANKFSTYADALWWGTITLTITIGYGDKTELTWLGRLA
 consensus AWYIGFLVLIF SPLVYL EKDAN FSTYAD LWWGTITLTITIGYGDTE TWLGRIL

KCN6q_ AGFALLGISFFALPAGILGSGFALKVQEOHROKHFEKRRNPAANLIQCVWRSSVAADKES
 KCNQ4_ AGFALLGISFFALPAGILGSGFALKVQEOHROKHFEKRRNPAANLIQAAWRLNSTD.MSR
 consensus AGFALLGISFFALPAGILGSGFALKVQEOHROKHFEKRR PAANLIQ WR Y De Sr

KCN6q_ .VSIATWKP...HLK.....ALH.....TCs
 KCNQ4_ AYLTATWYYVDSILPSFRELALLFEHVORARNGGLRPLEVRRAPVPDGAPEYPPVATCH
 consensus a ATW yds L sfrelAL fehvqarngglrplevrrapvpdgapeyppvatC

KCN6q_ .P..TKKEQGEASSSQKLSFKERVRRMASP.R..GOSIKSRQASVGDRRSPSMTITTE.S
 KCNQ4_ RPGSTSPCPGE..SSRMG.IKDRIRMGSSORRTGPS.KQQLAPPTMPTSPSSEQVPEATS
 consensus rPgST GEASSS s KERVRRmas qRrtG sIK A SPSTd aBgts

KCN6q_ PTKVOKSWSFNDRTRFRSLRLKSSOPVIDATLCTDDVYDEKGCOCVYVLDITFP
 KCNQ4_ PTKVOKSWSFNDRTRFRSLRLK...PE..TSAEDAP.HETVAEKSVOCPVVDKMPA
 consensus PTKVOKSWSFNDRTRFR SLRLKssqKpV Ad A gtdDV dEK QcdvsVdI P

KCN6q_ IKTIVIRAIRINKFHVAKRKFKETLRPYDVKDVEIOYSAGHLDMLCRIKSLQTRVDQILGK
 KCNQ4_ IKTIVIRIRIMKFVAKRKFKETLRPYDVKDVEIOYSAGHLDMLCRIKSLQTRVDQILGK
 consensus IKTIVIRIRIMKF VAKRKFKETLRPYDVKDVEIOYSAGHLDM LRIKSLQTRVDQILGK

KCN6q_ GOITSDEKSREK...ITAEHETTDLSMIGRVVKVEKQVOSIESKLDCLLDIYQOVLRKG
 KCNQ4_ G...PGDKAREKGDKGPSDAEVVDLSMIGRVVKVEKQVOSIEHKLDLLGLFYSRCLRS
 consensus Gqi DkK REKgdK e E DdLSMIGRVVKVEKQVOSIE KLD LL Y LR C

KCN6q_ .SASALALISFOYPPFECQTSQDYSPVDSDKISGSAQ.NSGCISRSSTANISRGLOFII
 KCNQ4_ TSAS...LGAVQVPLEFDPDITSQDYSPVDHEDISVSAOTLS..ISRSVSTNAD.....
 consensus tSASalaLa QIP Fe e TSDY SPVD DLS SAQT SgcISRS S N1 rglqfil

KCN6q_ TPNEFSAQTFYALSPTMHSQATQVPISQSDGSAAVATNTIANQINTAPKPAAPTTLQIPP
 KCNQ4_
 consensus tpnefsaqtfyalsptmhsqatqvpiqsdsavaatntianqintapkpapttlqipp

KCN6q_ PLPAIKHLPRPETLHPNPAGLOESISDVTTCLVASKENVOVAQSNLTKDRSMRKSFDMSG
 KCNQ4_
 consensus plpaikhlprrpetlhpnpagloesisdvttclvaskenqvvaqsnltkdrsmrksfdmsg

KCN6q_ ETLLSVCPMVPKDLGKSLSVQNLIRSTEELNIQLSGSESSASRGSDFYPKWRESKLFIT
 KCNQ4_
 consensus etllsvcpmvpkdlgkslsvqnlirsteelniqlsgsessasrgsqdfypkwresklfit

KCN6q_ DEEVGPEETETDTFDAAPOPAREAAAFASDSLRTGRSRSSOSICKAGESTDALSLPHVKLK
 KCNQ4_
 consensus deevgpeatetdtfdaapqpareaafasdslrtgrsrssosickagestdalslphvklk

FIGURE 4B

KCN6q_ LGPPPGD APRALVLTAVQSE QGELGG
 KCNQ4_ LGPPPGD APRALVLTAVQSE QGELGG
 KCNQ2_ NGGVYPG PSCEKKLVG FVGLDFCAPDSTRDCAII
 KCNQ3_ GAAGCGGCGGGGGAANPAGGDAAGDEERKVGILAPG DVEQVTLALG
 KCNQ1_
 consensus ma k zr gaag gg pg gggaa pag al ag er vgl pgapd g alg

KCN6q_ LGGKPLS YTS SQS . CR . RN VK . YRRMONT
 KCNQ4_ LGGKPLS YTS SQS . CR . RN VK . YRRMONT
 KCNQ2_ EAPKRGSI LSKP RAGG AGAG R PPKRN AF . YRRMONT
 KCNQ3_ ADKDGALLLEGGGRDEGORRTEOGIGLLAKTPLSRPVKRNN AK . YRRMONT
 KCNQ1_
 consensus agspr a lgspls gagr gqzrtg gsgllakts s kRnsaaakryrrlQnyl

KCN6q_ YHAFVFLLVFCCLILSVFSTIPEHTKLA SCLLILEFVMIVVFGLE
 KCNQ4_ YHAFVFLLVFCCLILSVFSTIPEHTKLA SCLLILEFVMIVVFGLE
 KCNQ2_ YHAFVFLLVFCCLILSVFSTIPEHTKLA SCLLILEFVMIVVFGLE
 KCNQ3_ YHAFVFLLVFCCLILSVFSTIPEHTKLA SCLLILEFVMIVVFGLE
 KCNQ1_
 consensus YnvLERPrGWacfiYHafvFLlvf CLilsvlstikeyeklasgcLlile vmivvFGLE

KCN6q_ YIRIWSAGCCCRYGW GRIRFARKPFCEVIDTIVLIAS AVV . SAK . QGN . FATSALRSI
 KCNQ4_ YIRIWSAGCCCRYGW GRIRFARKPFCEVIDTIVLIAS AVV . SAK . QGN . FATSALRSI
 KCNQ2_ YIRIWSAGCCCRYGW GRIRFARKPFCEVIDTIVLIAS AVV . SAK . QGN . FATSALRSI
 KCNQ3_ YIRIWSAGCCCRYGW GRIRFARKPFCEVIDTIVLIAS AVV . SAK . QGN . FATSALRSI
 KCNQ1_
 consensus yivriWSAGCCcrYrGW GRIRFARKPFCEVIDTIVLIASIAVvaagtqGnvfATSALRSI

KCN6q_ RFLQILRM RMDRRGCTWKLLGSSVVAHASKELITAWYIGFLVLIFSSFLVYLVEKD
 KCNQ4_ RFLQILRM RMDRRGCTWKLLGSSVVAHASKELITAWYIGFLVLIFSSFLVYLVEKD
 KCNQ2_ RFLQILRM RMDRRGCTWKLLGSSVVAHASKELITAWYIGFLVLIFSSFLVYLVEKD
 KCNQ3_ RFLQILRM RMDRRGCTWKLLGSSVVAHASKELITAWYIGFLVLIFSSFLVYLVEKD
 KCNQ1_
 consensus RFLQILRMvrmDRRGCTWKLLGSSvvaHskELItawYIGFLvLifssflvYLAEKD v

KCN6q_ ANKEFSTYADALWWG ITLTTCYGDKTP TWLGRLLIS AC FAL GISSFFALPAG
 KCNQ4_ ANKEFSTYADALWWG ITLTTCYGDKTP TWLGRLLIS AC FAL GISSFFALPAG
 KCNQ2_ ANKEFSTYADALWWG ITLTTCYGDKTP TWLGRLLIS AC FAL GISSFFALPAG
 KCNQ3_ ANKEFSTYADALWWG ITLTTCYGDKTP TWLGRLLIS AC FAL GISSFFALPAG
 KCNQ1_
 consensus dagge andefstyADALWWGItltTTCYGDKTPqTWlGrllaa FtlLgISFFALPAG

KCN6q_ ILGSGFALKVQEOHROKHFEKRRNPAANLIQCVWHSYAADEKS VSIATWKP HL
 KCNQ4_ ILGSGFALKVQEOHROKHFEKRRNPAANLIQCVWHSYAADEKS VSIATWKP HL
 KCNQ2_ ILGSGFALKVQEOHROKHFEKRRNPAANLIQCVWHSYAADEKS VSIATWKP HL
 KCNQ3_ ILGSGFALKVQEOHROKHFEKRRNPAANLIQCVWHSYAADEKS VSIATWKP HL
 KCNQ1_
 consensus ILGSGFALKVQeqhRQKHfEkrrnpAanLIQaawRfYatd psr dl aTWkye vtl

KCN6q_ K ALH TCS PL TKKE
 KCNQ4_ K ALH TCS PL TKKE
 KCNQ2_ K ALH TCS PL TKKE
 KCNQ3_ K ALH TCS PL TKKE
 KCNQ1_
 consensus p frklp L qrarnggllrplevrrapvpdgapsryppvatcargp aftk

KCN6q_ QCEASSSOK SPKSRVMA R COSIKSRQASVGDHRSPTDITAE SP KVQKSW
 KCNQ4_ QCEASSSOK SPKSRVMA R COSIKSRQASVGDHRSPTDITAE SP KVQKSW
 KCNQ2_ QCEASSSOK SPKSRVMA R COSIKSRQASVGDHRSPTDITAE SP KVQKSW
 KCNQ3_ QCEASSSOK SPKSRVMA R COSIKSRQASVGDHRSPTDITAE SP KVQKSW
 KCNQ1_
 consensus p apssSgklslkdrvrmsppqrgvvp gKl tap tmrrspstd t Eatsptkv kaw

KCN6q_ SFNDRTRFRPSLRKSS QPKPIDANTALG TDDVYDEKGCQCDVYEDLTPPLKTVIRA
 KCNQ4_ SFNDRTRFRPSLRKSS QPKPIDANTALG TDDVYDEKGCQCDVYEDLTPPLKTVIRA
 KCNQ2_ SFNDRTRFRPSLRKSS QPKPIDANTALG TDDVYDEKGCQCDVYEDLTPPLKTVIRA
 KCNQ3_ SFNDRTRFRPSLRKSS QPKPIDANTALG TDDVYDEKGCQCDVYEDLTPPLKTVIRA
 KCNQ1_
 consensus sfndtrtrfrt rlggsapr vqs ada pgddvadek qcdfsvedltpalk vira

FIGURE 4C

KCN6q_ IRIIMFELVAKRRKFETLRPYDVKDVIEQYSAGHLDMLCRIKSLQTRVDQIYVCG...ITSD
 KCNQ4_ IRIIMFELVAKRRKFETLRPYDVKDVIEQYSAGHLDMLCRIKSLQTRVDQIYVCG...PGD
 KCNQ2_ YCIRMFELVSKRRKFESLRPYDVMDVIEQYSAGHLDMLSRIKSLQTRVDQIYVCG...GEAETDK
 KCNQ3_ YRIICQIRSIYKIKFETLRPYDVKDVIEQYSAGHLDMLSRIKSLQTRVDQIYVCG...ITPGPPSPK
 KCNQ1_ IRRMQTFVAKSKFQQARQPYDVMDVIEQYSAGHLDMLSRIKSLQTRVDQIYVCG...LF
 consensus irimkflvaKrKPKetlrPYDVkDVIEQYSAGHLdmlsRIKsLQtrvDqiYvgkq it

KCN6q_ KRSREK.....ITAFETTD.....DSHMGGRVVKVEKQVOS...ESKLECD
 KCNQ4_ KAREKGDK.....GPSDAEVD.....SHMGGRVVKVEKQVOS...EHKLDLM
 KCNQ2_ D...RTKG.....PAEAEP.....EDPSHMGRCVKVEKQVLSMEKKLDPL
 KCNQ3_ HKKSOKGSAETEPSOOSPRNPEYVAR...STSEIEDOSHMGKRVKVEKQVODMCKKLDPL
 KCNQ1_ ISVSEK.....SKDR.GSN.....SGARHNRVEDKVTQIQONALET
 consensus kk reKg ftfpsqqsprn p eaavp seiadlammgrvkvkVEkqvQsleklid il

KCN6q_ DRYOQVLRKG.SASAAALNSFOKPPFECEOTS DYQSPVDSK...DLGCSAQ.NSGCFSRS
 KCNQ4_ GFYSRCILRSCTSAS...LHAYOPLDPEITS DYHSPVDHE...DSVSQAOTLS...IGRS
 KCNQ2_ NRYMQRMG...IPPTETRY...FOKDEPAPFFVHSPEDSKHEHMDRHCIV...KIVRS
 KCNQ3_ DHHQHEK...LOVQTEYMTKGTSSPAEAE...KKEDNA...SDOK.....TEICH
 KCNQ1_ DILLHQLSLHGGSYPCAGCFDREGGAHITQPCGSGGSVDPELEHPSNTLPTTYEQI...PFR
 consensus diymqvrlkg sas lt appqigafepaq sdyhspvDak yvdlgsaq s tiara

KCN6q_ TSANISRGLOFILTENPFAOTFYALSETMHSQATQVPTSSQSDGSVAATUTIAQINQA
 KCNQ4_ VSTNMD.....
 KCNQ2_ SSTGOK...NFSAPBA...PVQCPSST...SWQ.....PQSHPRGCHGTS
 KCNQ3_ YSETG.....PPE.....PYSFHOVVIDKSPYGYFAHDVNLPR.C.GPS
 KCNQ1_ GPDECS.....
 consensus ts garglq ppe saqtifyalpp q t is a p a prag gts

KCN6q_ EKPAFTTLOIPDPLPAIKHPRPEZTHPNPAGLOESISDVTTCLVASKENVOVAOSHLT
 KCNQ4_
 KCNQ2_ PV.GDHGSLVRIEPPDAH...ER...SLSAYCGEN.....RASMEPT...RQEDTP
 KCNQ3_SKVQATPSSATTTTHERETVPILTLLDS.....RVSCHS.....QADLQ
 KCNQ1_
 consensus p pa gtlq pp pa larp tl ag esisdvttclras a vqv q dl

KCN6q_ KDRSMKSPDMGGETL SVCPMVPRDLCKST.SVONLIRSTEELNIQLSGSESSASHGSO
 KCNQ4_
 KCNQ2_ G.....CRPPECNLR...D...SDTSKSTPSVD...HEELERSPSGFSISOS...NL
 KCNQ3_ GPYSDRISPRORRSITR...D...SDTFISLMSVN...HEELERSPSGFSISODR...
 KCNQ1_
 consensus g s r s r tlrsvcpdvpsdt isl svqnlirsheelers sgfsisqara

KCN6q_ DLYPKWRESKLETTTEEVGPEETEDDFDAAPQ.....AREAFASDSRTGRSSSS
 KCNQ4_
 KCNQ2_ DALNSCYLVAPCAKVRVFAEGESDITDLDLCTPCGPPERSATGEGPFGDVGNAGPRK...
 KCNQ3_ DRYFGPNHGSNNREKR...FAEGETDITDLPFTBSCSMPLSSTGCG.ISDSVWTFSEKPI
 KCNQ1_
 consensus dfl aa fi d r ylaegetdtdsd tp g p satgag sdslwtg k

KCN6q_ OSICKAGESTDALSLPHVKLK
 KCNQ4_
 KCNQ2_
 KCNQ3_
 KCNQ1_
 consensus qsickagestdalslphvklk

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/09587

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07K 1/00, 16/00; G01N 33/53

US CL : 530/350, 387.1; 435/7.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/350, 387.1; 435/7.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	KANANURA et al. The new voltage gated potassium channel KCNQ5 and neonatal convulsions. NeuroReport. June 2000 Vol. 11, No. 9, pages 2063-2067, see entire document.	1-10
Y	WANG et al. KCNQ2 and KCNQ3 Potassium Channel Subunits: Molecular Correlates of the M-Channel. Science. 04 December 1998, Vol. 282, pages 1890-1893, see entire document	1-21

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

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04 AUG 2000

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